EARLY HOSPITAL READMISSION FOLLOWING KIDNEY TRANSPLANTATION AND SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

by
Elizabeth King

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ABSTRACT

In the United States, 30% of kidney transplant (KT) recipients experience early hospital readmission (EHR), or readmission within 30 days of discharge following transplantation. Known predictors of EHR include older age, African American race, comorbidity, and increased length of stay, and EHR is associated with inferior patient and graft survival.

To broaden our understanding of EHR in transplantation, we began with a prospective cohort study of EHR among KT recipients at Johns Hopkins Hospital. We used granular clinical data to characterize clinical scenarios leading to EHR. We also explored the association between EHR and novel predictors, including cognitive function, physical function, and socioeconomic factors.

Next, we used national data to further explore novel predictors of EHR and to determine whether the risk of adverse outcomes associated with EHR varies over time. We used County Health Rankings and U.S. Census data to quantify the association between EHR and social determinants of health. We then estimated the association between EHR and adverse outcomes for two distinct time periods: during the EHR hospitalization and post-EHR. Finally, we used national data to develop a risk prediction model for EHR following simultaneous pancreas-kidney (SPK) transplantation and to quantify the association between EHR and post-SPK outcomes.

At our center, we found that a high number of KT recipients are readmitted directly to the hospital without prior evaluation by a healthcare provider. Using national data, we found that living in a high-risk community increases the risk of EHR, but socioeconomic status was not associated with EHR. Following SPK, we found that 55% of recipient experience EHR. EHR following SPK was associated with younger recipient age, African American donor, and length of stay. We also found that EHR, following both KT and SPK, was most strongly associated with

graft loss and mortality during the readmission hospitalization, but also portends a lasting, albeit attenuated, risk post-readmission.

Our future plans include the development of a clinical prediction tool to assess recipient risk of EHR prior to transplant discharge. We plan to develop of clinical strategies and outpatient resources aimed at decreasing the risk of EHR.

THESIS READERS:

Dr. Dorry Segev, Professor, Clinical Investigations, Surgery

Dr. Jennifer Dodson, Assistant Professor, Clinical Investigations, Urology

Dr. James Tonascia, Professor, Biostatistics

Dr. Charles Flexner, Professor, Clinical Investigations, Clinical Pharmacology

Dr. Niraj Desai, Assistant Professor, Surgery

Dr. Brian Caffo, Professor, Biostatistics

Dr. Marie Diener-West, Professor, Biostatistics

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INTRODUCTION

Early hospital readmission (EHR), defined as readmission within 30 days of initial discharge, is a known predictor of potentially avoidable morbidity, mortality, and cost. EHR is increasingly used a marker of healthcare quality. In 2009, the Centers for Medicare and Medicaid Services (CMS) began publicly reporting hospital readmission rates to motivate clinical practices that reduce EHR. In 2012, CMS began the Hospital Readmission Reduction Program (HRRP), which financially penalizes hospitals with higher than expected rates of readmission. However, critics of the HRRP argue that the majority of readmissions may not be preventable and many readmissions actually represent good clinical care. A comprehensive understanding of EHR will enable more appropriate clinical practice and guide future healthcare policy.

Following general surgical procedures, readmission is as high as 22%. Identified risk factors for readmission include comorbidity, length of stay, and surgical complications, and EHR is associated with increased postoperative mortality. Following kidney transplantation, 31% of KT recipients experience EHR. Many argue that KT is surgically complex and EHR is a marker of clinical complexity rather than inferior quality. However, there is a high level of variability in the rate of readmission across transplant centers, ranging from 18-47%.

To understand EHR following KT, it is first necessary to identify, which patients are at highest risk of readmission. Using national data, our group previously identified 19 patient-level characteristics associated with EHR. Recipient factors included African American race and various comorbidities, while transplant factors included extended criteria donor, lack of induction immunosuppression, and increased length of stay. Despite these patient-level associations, it remains difficult to predict which patients will experience EHR, and even after adjusting for clinical characteristics, there is still wide variation in the incidence of EHR across transplant

centers. Factors above and beyond clinical predictors, including healthcare practices, socioeconomic factors, and the environment in which the patient lives, may contribute to EHR.

To better address EHR, we must understand the immediate and long-term impact of readmission on post-transplant outcomes. Our group showed that recipients experiencing EHR are more likely to experience late hospital readmission or subsequent readmission within the first-year post-transplant. In addition, KT recipients with EHR have an increased risk of death-censored graft loss and mortality. Although EHR increases the risk of adverse outcomes, the timeline of risk is unclear. Understanding the attributable risk associated with EHR during different time periods, specifically the EHR hospitalization and post-EHR, may help guide clinical management.

Little is known about EHR following simultaneous pancreas-kidney transplantation (SPK), which is an important treatment option for Type 1 diabetics with end stage renal disease. SPK is surgically more complex and the incidence and risk profile associated with EHR may be unique given the increased complexity. Existing studies suggest readmission is much more common among SPK recipients, but fail to identify relevant risk factors for EHR and have yet to classify the impact of EHR following SPK.

The goals of this thesis were to identify systematic mechanisms of EHR, to provide transplant providers with a more comprehensive profile of recipients at risk of EHR, and to accurately quantify the impact of EHR on long-term post-transplant outcomes. Chapter 1 describes the clinical scenarios surrounding EHR using granular clinical data from our transplant center. Chapter 1 also explores novel risk predictors for EHR including health related quality of life, cognitive function, functional status, physical disability, socioeconomic factors, and desensitization. Chapter 2 quantifies the association between EHR and social determinants of health, assessing the effect of community risk, socioeconomic status, residential status, and

distance from transplant center on EHR. Chapter 3 evaluates the association between EHR and post-KT survival, isolating the risk associated with EHR during the EHR hospitalization and the risk post-EHR. Chapter 4 explores the incidence of EHR following SPK and quantifies the association between patient-level characteristics and EHR. Finally, Chapter 5 quantifies the impact of EHR on post-SPK survival.

We hope this thesis work will guide development of interventions that can effectively mitigate the risk associated with EHR.

CHAPTER 1: READMISSION FOLLOWING KIDNEY TRANSPLANTATION – SINGLE CENTER

SUMMARY:

Based on national data, 30% of kidney transplant recipients experience early hospital readmission. Unfortunately, registry data lack the granularity to identify mechanisms of readmission and risk factors beyond clinical characteristics. The purpose of this study was to broaden our understanding of 30-day readmissions through an in-depth analysis of single-center data. We studied 400 adult, kidney-only transplant recipients from May 1, 2012- April 30, 2014. Modified Poisson regression was used to estimate the association between readmission and novel predictors (health related quality of life, cognitive function, functional status, physical function, socioeconomic factors, and desensitization). Interestingly, 40.8% of recipients experiencing readmission were readmitted directly from home. The most common reason for readmission was infection (24.2%), however 16% of readmitted recipients had two or more primary reasons for readmission. Readmission was not associated with health-related quality of life, cognitive function, functional status, physical function, socioeconomic factors, or desensitization. Readmission was associated with temporary housing during the immediate post-transplantation period (aRR $_{1.56}2.56_{4.20}$, $p<0.001$). At our center, almost half of readmissions occurred directly from home, without prior evaluation by a healthcare provider. The reasons for readmission were similar to those in national data, however 16% of readmissions occurred due to more complex scenarios.

INTRODUCTION

National registry data demonstrate that 31% of kidney transplant recipients experience early hospital readmission (EHR), or readmission within 30 days of initial discharge after kidney transplantation (KT) (1). Based on this data, we recently identified recipient and transplant factors that increase the risk of EHR, including advanced age, African American race, obesity, diabetes, time on dialysis, extended criteria donor (ECD), donation after cardiac death (DCD), and length of stay greater than 5 days (1). EHR has a significant impact on post-transplant outcomes, such that EHR is associated with inferior graft and patient survival (2). Unfortunately, national registry data are unable to capture more granular details about recipients experiencing readmission and the readmission process itself. As such, we have been unable to investigate patient-level contributors, beyond clinical characteristics, that may have an important impact on EHR.

Single center studies can be very useful for identifying clinical details and processes not captured in registry data. With respect to EHR, single center studies have already provided a more comprehensive understanding of medical reasons for readmission and an initial understanding of which readmissions may be preventable (3-5). For example, in a single center study of 462 KT recipients, Lubetzkety et al. established that 20.7% of readmissions were due to issues with the surgical site and that 11.7% of readmitted recipients had a medical issue at the time of initial discharge that ultimately lead to readmission (3). Another study of 753 KT recipients used single center data to show that a mere 8% of readmissions were preventable (4). Single center data can also provide more granular details about patient-level risk factors. Our own group used single center data to demonstrate an association between frailty and EHR. Frail KT recipients were much more likely to experience EHR (45.8% vs. 28.0%, $p = 0.005$) (5). Many patient-level characteristics that contribute to post-transplant outcomes are impractical to measure nationally. In particular, factors such as health related quality of life (HRQOL), cognitive and physical

function, and socioeconomic status are not captured by national registries, but may contribute to EHR. Single center data may be necessary to broaden our understanding of EHR.

To better predict which recipients are at risk of EHR and to understand the mechanism through which EHR occurs, we performed a single center prospective study of EHR following KT at our high volume center. The objective of this study was to characterize the route of readmission and to quantify the association between EHR and novel predictors including HRQOL, cognitive and physical function, and socioeconomic factors.

METHODS

Study Population

This was a prospective cohort study of 251 adult kidney-only transplant recipients, supplemented with data from a retrospective cohort of 149 adult kidney-only transplant recipients, for a total study population of 400 recipients that underwent transplantation at Johns Hopkins Hospital, Baltimore, Maryland between May 1, 2012 and April 30, 2014. Two recipients died within 30 days following discharge after KT; one was not readmitted prior to death and was excluded from the study. The other was readmitted prior to death and therefore was included in the study. Recipient, donor, and transplant characteristics (age, sex, race, body mass index (BMI), diabetes, hepatitis C seropositivity, time on dialysis, donor type, KT length of stay) were ascertained from medical records. The Johns Hopkins Institutional Review Board approved this study.

Ascertainment of Exposures

HRQOL, cognitive function, activities of daily living/instrumental activities of daily living (ADLs/IADLs), and physical function were prospectively assessed immediately prior to KT. These exposures were measured on 251 of the 400 participants. HRQOL was assessed using a single question from the Kidney Disease Quality of Life (KDQOL) instrument: “In general would

you say your health is…" The question is answered on a 5-point Likert scale ("excellent", "very good", "good", "fair", or "poor") (6). Cognitive function was assessed using the Modified Mini Mental State (3MS) test. Total scores of the 3MS range from 0 to 100 with lower scores indicative of a higher level of cognitive impairment. Scores <79 are indicative of some cognitive impairment and scores <48 are indicative of severe cognitive impairment (7). ADLs were self-reported by recipients based on the Katz ADL Index, which assesses six different tasks: bathing, dressing, toileting, transferring, continence, and feeding. A point is given for each task that can be carried out by the recipient without assistance. The sum ADL score ranges from 0 to 6, and lower scores are indicative of a higher level of functional dependence (8). A priori, ADL functional dependence was defined as requiring assistance with one or more task, or a score less than or equal to 5. IADLs were self-reported by recipients based on the Lawton IADL scale, which assesses eight tasks: ability to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medication, and ability to handle finances. The sum IADL score ranges from 0 to 8, and lower scores are indicative of a higher level of functional dependence (9). A priori, IADL functional dependence was defined as requiring assistance with one or more tasks, or a score less than or equal to 7. Physical function was assessed using two measures: the Short Battery of Physical Performance (SBPP) and grip strength. The SBPP includes an assessment of standing balance, a timed 8-foot walk at normal pace, and a timed test of 5 repetitions of rising from a chair and sitting down. The sum score ranges from 0 to 12, with lower scores indicating worse physical function (10). A priori, physical disability was defined as a score less than 8 on the SBPP. Grip strength was directly measured and adjusted for gender and BMI to give a grip strength rating with higher values indicating more strength (11).

Economic factors (fixed income, employment status, insurance status, financial issues) and social factors (marital status, education level, cohabitants, intravenous drug use (IVDU), and legal

issues) were ascertained from medical records. We also identified patients who, because of traveling from out of town for transplantation at Johns Hopkins, arranged temporary housing in Baltimore during their convalescence instead of recovering at home.

Ascertainment of Outcome

Early hospital readmission was defined as any hospitalizations within 30 days of initial discharge following kidney transplantation, as done in our previous national studies (1, 2, 5, 12). At the time of readmission, the nurse practitioner caring for each recipient was asked to document the route of readmission and reason for readmission. Missing information about route and reason were ascertained through medical record abstraction. Two physicians performed independent review of each readmission to resolve any discrepancies and to determine a single primary reason for readmission. For recipients readmitted more than once in the 30-day period following KT discharge, the reason and route for their first readmission were used.

The route of readmission was empirically classified into one of six categories: direct admission from home, admission from the emergency department, admission from clinic, transfer from an outside hospital, transfer from a rehabilitation center, or other route. Route of readmission was also treated as a binary outcome to compare direct admission from home to admission via any other route. The decision to admit directly from home would have occurred without physical evaluation of the recipient by a healthcare provider, and was therefore treated as mechanistically distinct compared to any other route of readmission.

The reason for readmission was empirically classified into one of ten categories: infection, gastrointestinal disorder, fluid collection, hyperkalemia, graft rejection, volume overload, cardiac complication, genitourinary disorder/procedure, desensitization protocol, or other. The desensitization protocol category captures readmissions due to routine care of recipients that

received an incompatible KT. For patients who were found to have more than one reason for readmission, the two physician abstractors discussed each clinical scenario and agreed upon the most likely inciting reason for readmission.

Statistical Analysis

We compared differences in novel predictors between recipients experiencing EHR and recipient without EHR using t-tests for psuedonormally distributed continuous variables and chi-squared tests for categorical variables. The relative risk of EHR associated with each novel predictor was estimated using modified Poisson regression as previously described (13). Each predictor was first explored in a univariate model. Predictors that were statistically significant on univariate analysis were included in a final model adjusted for patient-level characteristics. For optimal parsimony, we adjusted the final model for recipient, donor, and transplant characteristics based on predictors of EHR in the national registry-based model including age, African American race, BMI, diabetes, time on dialysis, HCV, donor type, and length of stay (1). Functional forms for continuous variables were based on exploratory data analysis. Health related quality of life was dichotomized as "good" HRQOL or better and "fair" HRQOL or worse. Education level was dichotomized to compare high school education or less with any college education. Our center has a high proportion of KT recipients that require desensitization. A sub-group analysis was performed to characterize EHR among recipients undergoing desensitization. Confidence intervals are reported as per the methods of Louis and Zeger, as previously described (14, 15). All data were analyzed using Stata 14.0/MP for Linux (StataCorp LP, College Station, TX).

RESULTS

Study Population

Among the 400 KT recipients in this study, 120 (30%) had at least one EHR. Median time to EHR was 9 days (IQR 6-16), with 5% experiencing EHR within 3 days of discharge after KT,

11.6% within 7 days, and 21% within 14 days of discharge (Figure 1.1). The median length of the EHR hospitalization was 5 days (IQR 3-9) (Figure 1.2). The median age of recipients was 55 years (IQR 43.5-65), 44.8% were female, and 38.5% were African American (Table 1.1).

Route of EHR

The most common route of readmission was direct admission from home (40.8%) (Table 1.2). The proportion of patients directly readmitted from home was highest during the evening hours, with a nadir around midnight (Figure 1.3). When comparing recipients who were directly readmitted to those readmitted by any other route, there was no difference in age, sex, race, public insurance, transplant or readmission length of stay, or distance from transplant center (Table 1.3). A higher proportion of directly readmitted recipients had temporary housing, a finding that approached statistical significance on univariate analysis (26.5% vs. 12.7%, p=0.054).

Reason for EHR

The most common reason for EHR was infection (24.2%), followed by gastrointestinal complications (14.2%), and fluid collection (14.0%) (Table 1.4). Among those readmitted for infectious concerns, the most frequent causes were urinary tract infection (55.2%), bacteremia (17.1%), wound infection (13.8%), and *clostridium dificile* colitis (6.9%). Hyperkalemia comprised 9.2% of readmissions, with 9.1% of hyperkalemic recipients requiring inpatient dialysis. Another common reason for readmission was rejection. A total of 8.3% of recipients were readmitted for rejection. Among recipients readmitted for rejection, 90% had undergone desensitization. The "other" category included hyperglycemia, altered mental status, bleeding, gout, and fractures. Although categories were based on the single dominant reason for EHR, multiple reasons for readmission were identified for 16% of recipients.

HRQOL and EHR

Among participants that had HRQOL measured, 9.3% reported "excellent" HRQOL, 16.2% reported "very good" HRQOL, 40.5% reported "good" HRQOL, 26.3 reported "fair" HRQOL, and 7.7% reported "poor" HRQOL (Table 1.5). In univariate analysis, having HRQOL reported as "good" or better was not associated with EHR ($_{0.49}0.99_{1.98}$, p=0.9) (Table 1.6).

Cognitive Function and EHR

Among participants that had cognitive function measured, the median MMSE score was 94 (IQR 90-98) (Table 1.5). In univariate analysis, cognitive impairment (MMSE score<79) was not associated with EHR ($_{0.43}0.86_{1.75}$, p=0.7) (Table 1.6).

ADLs/IADLs and EHR

The median ADL score was 6 (IQR 6-6). ADL functional dependence, or an ADL score <6, was present in 10.5% of recipients (Table 1.5). In an unadjusted regression model, ADL functional dependence was associated with a 1.56-fold increase in the risk of EHR (RR $_{1.02}1.56_{2.40}$, p=0.04) (Table 1.6). In a multivariate model adjusted for recipient, donor, and transplant characteristics, ADL functional dependence was no longer associated with EHR (aRR $_{0.90}1.49_{2.47}$, p=0.8) (Table 1.7).

The median IADL score was 8 (IQR 8-8). IADL functional dependence, or an IADL score <8, was present in 11.7% of recipients (Table 1.5). In an unadjusted regression model, IADL functional dependence was not associated with EHR (RR $_{0.88}1.37_{2.14}$, p=0.2) (Table 1.6).

Physical Function and EHR

The median SBPP score was 11 (IQR 9-12). SBPP disability, or a score <8, was present in 1.3% of recipients (Table 1.5). In an unadjusted regression model, SBPP disability was not associated with EHR (RR $_{0.45}1.34_{4.00}$, p=0.6) (Table 1.6).

The median grip strength rating was 21 (15-30) (Table 1.5). In an unadjusted regression model, grip strength rating was not associated with EHR (RR $_{0.98}0.99_{1.01}$, p=0.4) (Table 1.6).

Socioeconomic Factors and EHR

Recipients experiencing EHR were similar to recipients without EHR with regard to most socioeconomic factors (Table 1.7). In univariate analysis, public insurance was associated with a 1.36-fold increase in the risk of EHR (RR $_{1.01}1.36_{1.84}$, p=0.046) (Table 1.6). In univariate analysis, temporary housing was associated with a 1.86-fold increase in the risk of EHR (RR $_{1.33}1.86_{2.61}$, p<0.001) (Table 1.6). No other socioeconomic factors were associated with EHR, including marital status, education level, employment status, mental health issues, drug use, or legal or financial issues. In a multivariate model adjusted for recipient, donor, and transplant characteristics, the association between EHR and temporary housing was even stronger, such that temporary housing was associated with a 2.56-fold increase in the risk of EHR (aRR $_{1.56}2.56_{4.19}$, p<0.001) (Table 1.7).

Desensitization and EHR

Desensitization was used for 28.6% of recipients. There was no significant difference in the crude incidence of EHR for recipients that underwent desensitization (35.5%) compared to other KT recipients (27.9%) (p=0.1). Among live donor KT recipients, desensitized recipients had a higher incidence of EHR (33.3%) compared to other live donor recipients (19.6%), a finding that approached statistical significance (p=0.08). Compared to other KT recipients experiencing EHR,

desensitized recipients were more likely to be readmitted for rejection (23.7% compared to 1.2%, $p<0.001$). Two desensitized recipients were readmitted for procedures that are part of our desensitization protocol, specifically gamma globulin infusion and replacement of a pheresis catheter. Compared to other KT recipients, desensitized recipients were more likely to be readmitted directly to the hospital without prior evaluation by a healthcare provider (55.3% compared to 34.2%, $p=0.03$).

DISCUSSION

In this single center study 30% of KT recipients experienced EHR. Direct admission from home was the route of readmission for 40.8% of recipients. Infection was the most common reason for readmission and 55.2% of infections were urinary tract infections. EHR was not associated with HRQOL, cognitive function, functional status, or physical function, although there was an association between EHR and ADL functional dependence on univariate analysis. Recipients with partial or total functional dependence (requiring assistance with at least one ADL) were at a 1.56-fold increased risk of EHR. Readmission was not associated with socioeconomic factors. However, readmission was associated with temporary housing. Recipients convalescing near the transplant center were at a 2.56-fold increased risk of EHR. The crude incidence of EHR among desensitized recipients was no different than the incidence for all other recipients or the incidence for other live donor recipients. Desensitized recipients experiencing readmission were more likely to be readmitted directly to the hospital and were more likely to be readmitted for rejection compared to all other recipients experiencing EHR.

To our knowledge, this is the first study to evaluate the route of hospital admission in the context of EHR. Nationally, direct hospital admission only accounts for about 15% of all non-elective adult hospitalizations (16). In our study, direct hospital admission was more common, occurring in 40.8% of readmissions. KT recipients require very specialized care immediately following

transplantation and they are monitored very closely as outpatients. Compared to other patients, KT recipients may maintain more frequent contact with their providers and may be less likely to present to the emergency department or another outpatient setting.

A strength of this study is that the reason for each readmission was ascertained directly from transplant providers or through medical record abstraction. Comprehensive evaluation of each readmission enabled us to more accurately determine the primary diagnosis. The most common reason for EHR was infection (24.2%) and the urinary tract was the most common source (55.2%). Our previous national model of EHR following KT showed 36% of readmissions were due to a kidney, ureter, prostate, or bladder procedure and only 12% of EHR was due to infection (1). However, that study was performed using Medicare claims data, which provides only broad categories for diagnoses and does not take into account the possibility of multiple reasons for one readmission. In another large single-center study of 201 KT recipients, Harhay et al. showed that 10.4% of readmissions were due to infection. Another 16.9% of readmissions were due to surgical complication, which included wound complications (4). In our study, wound complications due to infection were classified as infection.

We found that functional dependence, as measured through ADLs may be associated with an increased risk of EHR, although the association disappeared on multivariate analysis likely due to low sample size. The association is consistent with studies of functional dependence and readmission following other surgeries (17-19). In a study using National Surgical Quality Improvement Program (NSQIP) data for 10,112 patients undergoing joint athroplasty, partial or total functional dependence was associated with a 1.70-fold increase in EHR (17). Another study using NSQIP data found that among 35,655 patients that underwent laparoscopic weight-loss surgery, partial or total dependence was associated with a 1.94-fold increase in the risk of readmission (19). Health related quality of life and other measures of functional status were not

associated with EHR. One potential explanation is that candidates for KT are selected based on many of these same characteristics and our study population was relatively homogeneous with regard to HRQOL, cognitive function, and physical function.

Among desensitized recipients, the incidence of EHR was no different from other KT recipients. We might expect that desensitized recipients would be readmitted with increased frequency due the added complexity of desensitization, including changes in antibody status or issues with pheresis. The lack of difference may be attributable to the fact that in a center where many patients undergo desensitization we have outpatient resources in place for biopsies, antibody testing, and pheresis. In addition, these patients are monitored very closely as outpatients, and problems may be identified and treated early before they necessitate readmission.

Our study has several notable limitations. The results may not be generalizable given that transplant centers vary with respect to patient population and practice paradigms. However, our study population has similar demographics and a similar incidence of EHR compared to our previous national cohort. Additionally, compared to national models, our study has a relatively small sample size, which may limit our ability to find an association between novel predictors and EHR in multivariate analysis. However, even in univariate analyses few novel predictors were associated with EHR. Another limitation is that we were only able to measure HRQOL, cognitive function, and physical function on a subset of the study population. Recipients agreeing to participate in this portion of the study may be systematically different than recipients that did not participate. In fact, among recipients who participated, HRQOL was generally high and cognitive and physical disabilities were uncommon.

Using granular clinical data, our study has provided a deeper understanding of mechanisms of EHR. Readmission following KT is common and can involve complex clinical scenarios. Factors

beyond clinical characteristics may not be useful in predicting which recipients are at highest risk of readmission. The practice at our center appears to favor direct hospital admission to the transplant service. Evaluating recipients prior to readmission may help us determine which recipients actually require inpatient care and which can continue to be managed as outpatients.

Table 1.1: Study population characteristics, by early hospital readmission, n=400.

	No Early Hospital Readmission n=280	Early Hospital Readmission n=120	p-value
Median age, IQR (years)	54, 42-65.5	57, 46-64	0.5
Female, %	44.6	45.0	0.9
African American, %	40.0	35.0	0.3
BMI (kg/m2), %			0.8
Underweight (<18.5)	2.5	3.3	
Normal (18.5-25)	28.6	29.2	
Overweight (25-30)	30.7	33.3	
Obese (>30)	38.2	34.2	
Diabetes, %	21.1	25.0	0.3
Median dialysis vintage, IQR (years)	1.7, 0.1-3.6	2.7, 0.5-4.4	0.02
Hepatitis C positive, %	5.7	10.8	0.07
Donor type, %			0.7
Live	40.0	36.7	
Deceased standard criteria	44.3	47.5	
Deceased extended criteria	5.4	3.3	
Donation after cardiac death	10.4	12.5	
Desensitization, %	24.6	31.7	0.1
Median transplant length of stay, IQR (days)	9, 6-13.5	10, 8-19	<0.001
Median readmission length of stay, IQR (days)	-	5, 3-9	-

Table 1.2: Route of readmission.

	%
Direct admission from home	40.8
Emergency department	21.7
Clinic	17.5
Transfer from outside hospital	14.2
Transfer from rehabilitation facility	4.2
Other	1.7

Table 1.3: Recipient characteristics, by route of readmission. Direct admission is an admission directly from home without prior evaluation by a physician. Other routes included outpatient clinic, the emergency department, and outside facilities.

	Other Routes n=71	Direct Admission n=49	p-value
Median age, IQR (years)	57, 45-65	56, 45-62	0.5
Female, %	45.1	44.9	0.9
African American, %	39.4	28.6	0.2
Public insurance, %	60.6	51.0	0.3
Median transplant length of stay, IQR (days)	11, 8-20	10, 7-18	0.6
Median readmission length of stay, IQR (days)	5, 2-12	4, 3-7	0.3
Median distance from transplant Center, (miles)	36.9, 9.6-69.7	33.3, 16.6-129.3	0.3
Temporary housing for transplant, %	12.7	26.5	0.05

Table 1.4: Reason for readmission.

	%
Infection	24.2
Gastrointestinal	14.2
Fluid collection	14.0
Hyperkalemia	9.2
Rejection	8.3
Volume Overload	5.8
Cardiac	2.5
Genitourinary	2.5
Desensitization protocol	1.7
Other	20.0

Table 1.5: Health related quality of life, cognitive impairment, functional dependence, and physical disability, by early hospital readmission, by early hospital readmission. Health related quality of life (HRQOL) was measured on a Likert scale from "Poor" to "Excellent", cognitive impairment was defined as a mini-mental status test score <79, functional dependence was defined as requiring assistance with one or more activity of daily living (ADL) or as requiring assistance with 1 or more instrumental activity of daily living (IADL), and physical disability was defined as a short battery of physical function (SBPP) score less than 8.

	No Early Hospital Readmission	Early Hospital Readmission	p-value
Health related quality of life, %			0.02
Excellent	6.1	15.7	
Very Good	16.5	15.7	
Good	46.3	28.9	
Fair	23.2	32.5	
Poor	7.9	7.2	
Cognitive Impairment, %	6.1	5.0	0.7
Functional dependence ADLs, %	7.9	15.5	0.06
Functional dependence IADLs, %	9.8	15.3	0.2
Physical disability, %	1.1	1.7	0.6
Median grip strength rating	22, 16-30	21, 13-29	0.2

Table 1.6: Unadjusted relative risk of early hospital readmission following kidney transplantation, by each novel predictor. Each predictor was explored in a separate unadjusted model.

	RR	p-value
Fair or poor health related quality of life	$_{0.55}0.78_{1.11}$	0.2
Cognitive impairment	$_{0.43}0.86_{1.75}$	0.7
ADL functional dependence	$_{1.02}1.56_{2.40}$	0.04
IADL functional dependence	$_{0.88}1.37_{2.14}$	0.2
Physical disability	$_{0.45}1.34_{3.96}$	0.6
Grip strength rating	$_{0.98}0.99_{1.01}$	0.4
Public insurance	$_{1.01}1.36_{1.84}$	0.046
Fixed income	$_{0.67}0.93_{1.28}$	0.7
Married	$_{0.69}0.94_{1.28}$	0.7
College education	$_{0.83}1.15_{1.58}$	0.4
Employed	$_{0.64}0.86_{1.17}$	0.3
Living with cohabitants	$_{0.60}0.96_{1.53}$	0.9
IV drug use	$_{0.11}0.66_{3.87}$	0.6
Mental health issues	$_{0.85}1.17_{1.62}$	0.3
Legal issues	$_{0.06}0.41_{2.58}$	0.3
Financial issues	$_{0.77}1.12_{1.63}$	0.6
Temporary housing for transplant	$_{1.33}1.86_{2.61}$	<0.001

Table 1.7: Adjusted relative risk of early hospital readmission following kidney transplantation. Adjusted for recipient, donor, and transplant characteristics.

	RR	p-value
Age (per year)		
<40	$_{0.97}1.04_{1.11}$	0.3
40-70	$_{0.98}1.01_{1.03}$	0.5
>70	$_{0.76}0.87_{0.99}$	0.03
African American	$_{0.60}0.92_{1.40}$	0.7
BMI (kg/m2),		
Underweight (<18.5)	$_{0.52}1.04_{2.08}$	0.9
Normal (18.5-25)	REF	-
Overweight (25-30)	$_{0.59}0.93_{1.47}$	0.8
Obese (>30)	$_{0.55}0.89_{1.43}$	0.6
Females with diabetes	$_{0.36}0.76_{1.62}$	0.5
Males with diabetes	$_{0.54}0.93_{1.59}$	0.8
Dialysis vintage (per year)	$_{0.93}0.98_{1.03}$	0.4
Hepatitis C positive	$_{0.75}1.42_{2.71}$	0.3
Donor type		
Live	$_{0.36}0.71_{1.40}$	0.3
Deceased standard criteria	REF	-
Deceased extended criteria	$_{0.35}0.90_{2.32}$	0.8
Donation after cardiac death	$_{0.56}1.08_{2.06}$	0.8
Desensitization	$_{0.66}1.34_{2.75}$	0.4
Transplant length of stay		
<5 days	$_{0.43}0.91_{1.92}$	0.8
>5 days	$_{0.99}1.00_{1.02}$	0.4
ADL functional dependence	$_{0.75}1.30_{2.27}$	0.3
Public insurance	$_{0.87}1.29_{1.91}$	0.2
Temporary housing for transplant	$_{1.56}2.56_{4.19}$	<0.001

Table 1.8: Socioeconomic factors, by early hospital readmission.

	No Early Hospital Readmission	Early Hospital Readmission	p-value
Public insurance, %	45.7	56.7	0.04
Fixed income, %	37.8	35.3	0.7
Married, %	63.1	61.0	0.7
Education level, %			0.8
Some high school	4.5	5.2	
High school graduate	29.8	25.2	
Some college	21.5	23.5	
College graduate	26.4	31.3	
Post-collegiate degree	17.7	14.8	
Employed, %	48.6	43.3	0.3
Living with cohabitants, %	88.9	88.3	0.9
IV drug use, %	1.4	0.8	0.6
Mental health issues, %	25.4	30.0	0.3
Legal issues, %	2.7	0.9	0.3
Financial issues, %	16.8	19.2	0.6
Temporary housing for transplant, %	7.5	18.3	0.001

Figure 1.1: Percent of kidney transplant recipients experiencing early hospital readmission by day since discharge following transplantation. Three, 7-, and 9-day incidence of readmission represented by the vertical lines.

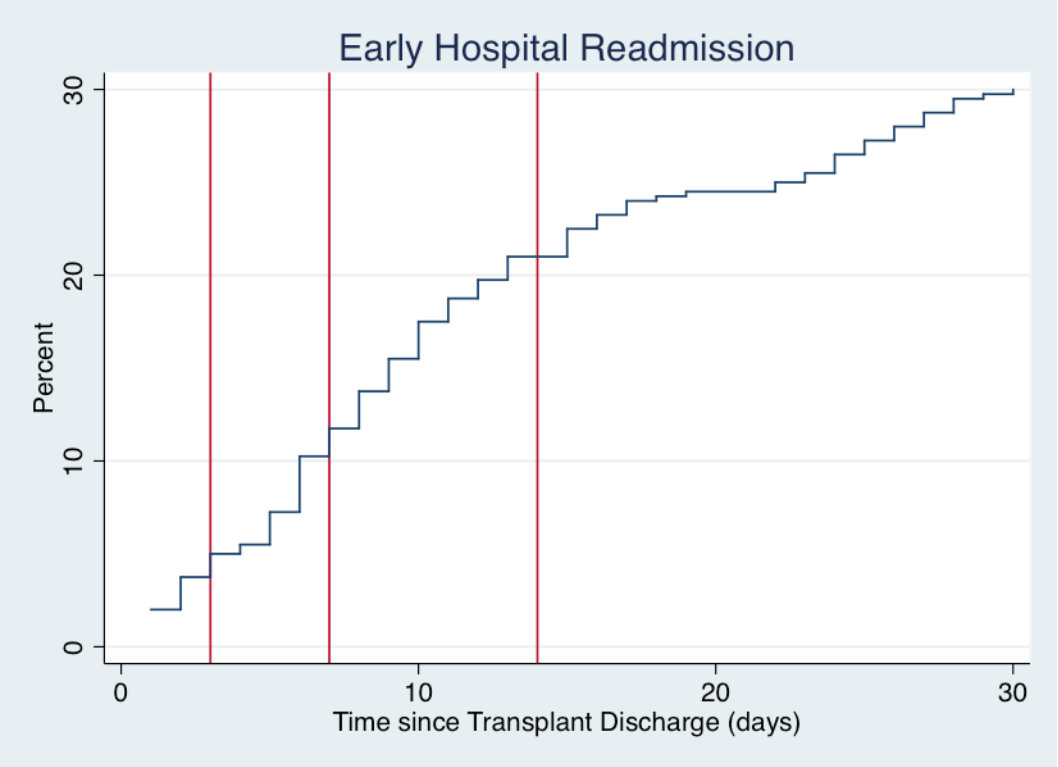


Figure 1.2: Length of stay for early hospital readmission hospitalization.

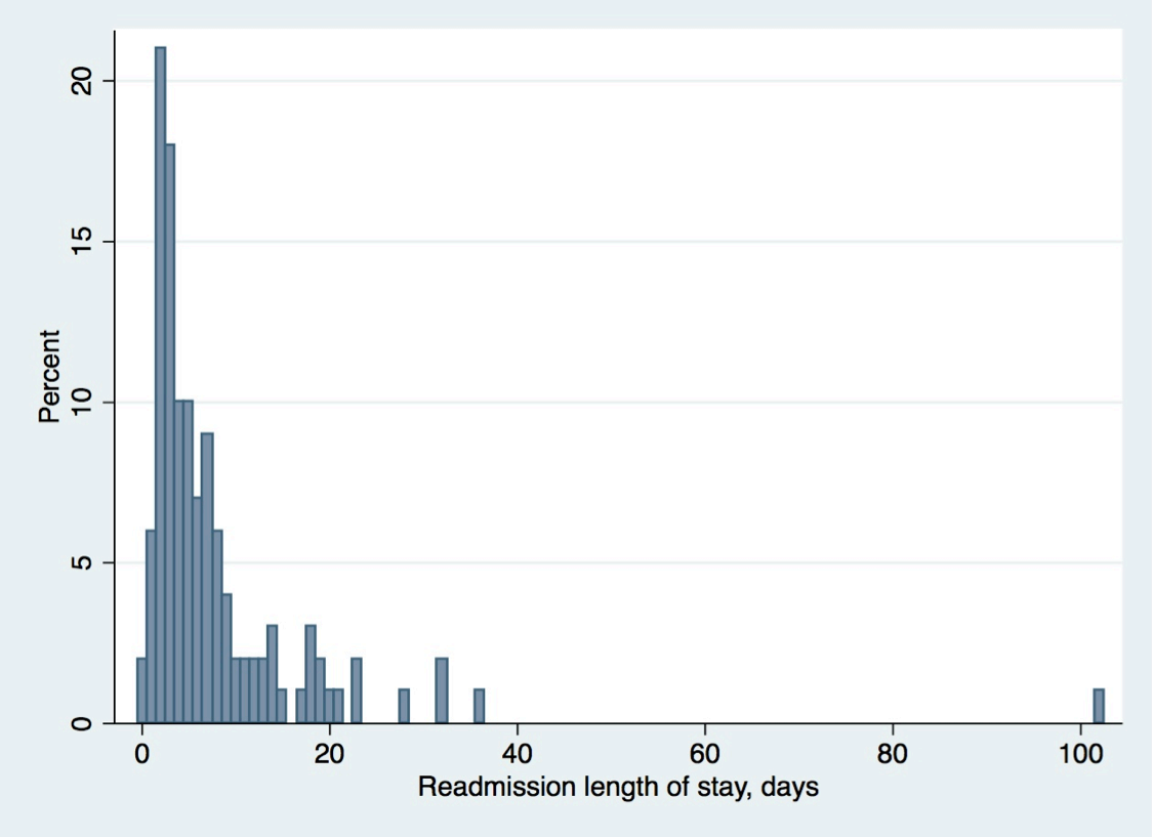
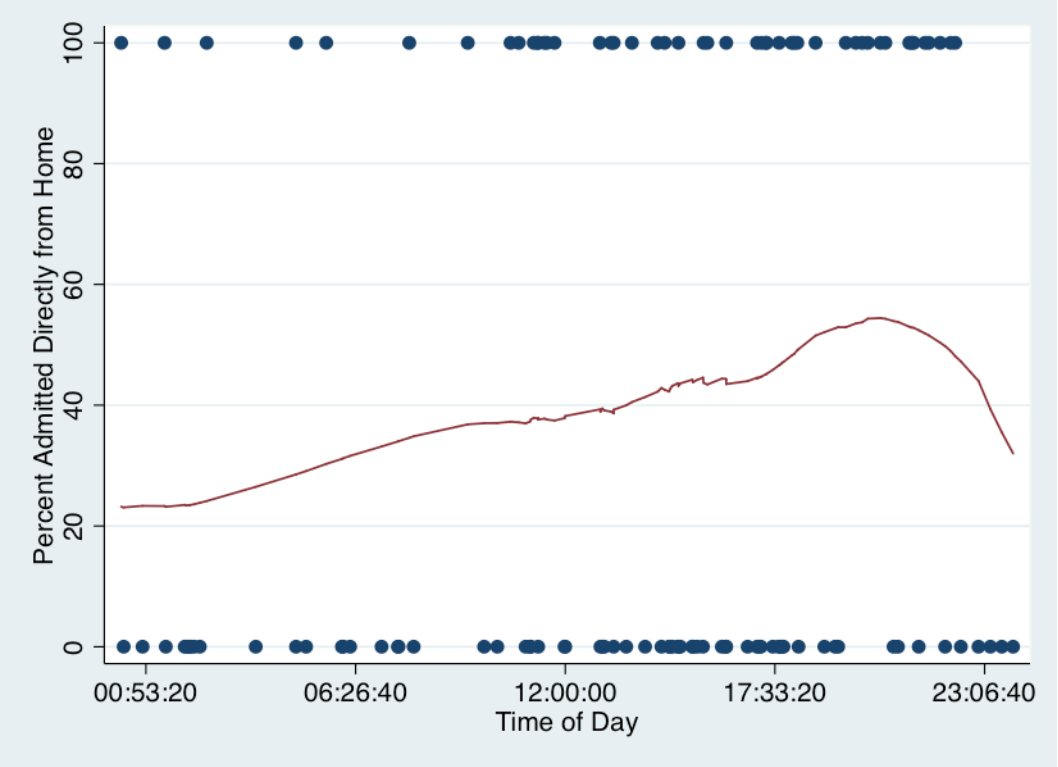


Figure 1.3: Proportion of direct admissions from home by time of day. Each dot represents one readmission. Dots at the top of the figure (y=100) are patients readmitted directly from home. Dots at the bottom of the figure (y=0) are patients readmitted through a different route. The plot represents the proportion of patients admitted directly from home at each time of day.



CHAPTER 2: SOCIAL DETERMINANTS OF HEALTH AND READMISSION

SUMMARY:

Early hospital readmission risk after kidney transplantation is high and, while associated with age, race, and comorbidity, difficult to predict. We hypothesized that social determinants of health, i.e. those above and beyond individual characteristics, may be associated with readmission. Medicare data was linked to county health rankings and census data to study 52,738 adult Medicare-primary first-time kidney-only recipients from December 1999-October 2011. Modified Poisson regression was used to estimate the association between 30-day readmission and community risk, socioeconomic status, residential setting, and distance to transplant center, adjusting for patient-level factors. Community risk was associated with readmission, such that living in low-intermediate, high-intermediate, and highest risk communities increased the risk of readmission (aRR $_{1.04}1.07_{1.11}$, aRR $_{1.02}1.07_{1.11}$, aRR $_{1.04}1.10_{1.16,}$ respectively) compared to living in lowest risk communities. There was no statistically significant association between readmission and socioeconomic status or readmission and residential setting. The risk of readmission was inversely associated with distance (<10 miles: reference, 10-90 miles: aRR $_{0.94}0.97_{0.99}$, 90-180 miles: aRR $_{0.86}0.90_{0.94}$, 180-240 miles: aRR $_{0.76}0.82_{0.89}$, >240 miles: aRR $_{0.74}0.94_{1.21}$). Factors above and beyond the individual, such as community risk and distance from the transplant center, should be considered in strategies to predict and reduce readmission following kidney transplantation.

INTRODUCTION

In the United States, 31% of kidney transplant (KT) recipients experience early hospital readmission (EHR), or readmission within 30 days of discharge following initial KT hospitalization (1). Early hospital readmission is important not only because of its burden to the patient and the medical system, but also as an independent predictor of both graft and patient survival (2). Patient-level clinical characteristics associated with EHR include age, African American race, various comorbidities, extended criteria donor, lack of induction therapy, and increased length of stay. However, despite these patient-level associations, it remains difficult for providers to predict which patients will experience EHR. We have explored center-level factors, hoping these would help explain which patients are at risk for EHR; however, despite wide center-level variation in the incidence of readmission following KT, conventional center-level characteristics are not associated with readmission (1).

A potential domain of risk contributing to EHR following KT is that of the environment in which the patient lives, rather than the attributes of the individual patient. Social determinants of health, such as access to care, socioeconomic status (SES), and home environment, influence health outcomes within the general population and even in transplant patients (20-28). For example, SES affects transplant access, such that high SES is associated with lower waitlist mortality or removal (aHR $_{0.84}0.86_{0.89}$) and higher access to live donor transplantation (aHR $_{1.70}1.76_{1.83}$) (27). Similarly, Schold et al. reported that among KT waitlist candidates, community risk, or the health behaviors of individuals living near transplant candidates and recipients, negatively impacts transplant access and outcomes. Candidates living in the highest risk communities have increased waitlist mortality (aHR $_{1.16}1.22_{1.28}$), decreased access to living donor KT (aOR $_{0.85}0.90_{0.94}$), and increased waitlist removal (aHR $_{1.22}1.36_{1.51}$). Even when candidates living in the highest risk communities achieve KT, they are at higher risk for post-KT mortality (aHR $_{1.13}1.26_{1.40}$) (25, 26).

The transition from inpatient to outpatient care following KT is complex, and we hypothesized that social determinants of health may contribute to readmission. Understanding risk factors beyond clinical characteristics can help predict which KT recipients are at highest risk for readmission and can also guide development of tailored interventions to prevent readmission (29, 30). The objective of this study was to evaluate the association between EHR and social determinants of health, specifically community risk, SES, residential setting, and distance from transplant center.

METHODS

Study Population and Ascertainment of Early Hospital Readmission

We studied 52,738 adult first-time KT recipients from December 1, 1999 through October 31, 2011 who had Medicare Part A and B as their primary insurance for at least 60 days before and 60 days following the date of transplant. Early hospital readmission was captured using United States Renal Data System (USRDS) claims data. As specified in our previously published model of EHR following KT, EHR was defined as at least one hospital readmission to any acute care hospital within 30 days of discharge after initial KT hospitalization (1, 2). KT recipients that died prior to discharge were excluded (n= 618). KT recipients that died within the first 30 days after KT were excluded (n= 105), unless EHR occurred prior to death (n= 222). Donor, recipient, and transplant characteristics were obtained from Organ Procurement Transplantation Network data.

Community Risk

County health rankings data were used to generate a community risk score for each recipient's county of residence based on ten health indicators (medial annual household income, prevalence of smoking, preventable hospitalizations, prevalence of physical activity, prevalence of adult obesity, prevalence of low birth weight, prevalence of poor physical health, prevalence of poor mental health, prevalence of poor/fair health, years of potential life lost), as previously described

(25, 26, 31). Potentially preventable hospitalizations are defined in this context as admissions to a hospital for acute illnesses or worsening chronic conditions that might have been avoided if a primary care provider in an outpatient setting had managed these conditions. For each of the ten indicators, the prevalence was categorized into quintiles and a cumulative score for each county was generated based on the sum of each quintile above the lowest risk category, or the first quintile, for each health indicator. For example, a county in the third quintile for each indicator would receive a risk score of 2 for each indicator, which results in a cumulative community risk score of 20. For regression modeling we also categorized community risk scores among recipients as lowest risk (score 0-10), low-intermediate risk (score 11-20), high-intermediate risk (score 21-30), and highest risk (31-40), based on previously published models of community risk.

Socioeconomic Status

U.S. Census data was used to generate a SES index corresponding to each recipient's zip code. The SES index was generated using the same method described by the Agency for Healthcare Research and Quality according to the formula $50 + (-0.07 \times \%\textit{crowded}) + (0.08 \times \textit{median property value}) + (0.11 \times \textit{median household income}) + (-0.10 \times \%\textit{poverty}) + (-0.11 \times \%\textit{education <12th grade}) + (0.10 \times \%\textit{college}) + (-0.08 \times \%\textit{unemployed})$, with possible values standardized to range from 0 to 100 (32). A higher index value corresponds to higher SES and a lower index value corresponds to lower SES. For regression modeling we also categorized SES among recipients into quartiles (lowest SES quartile, low-intermediate SES quartile, high-intermediate SES quartile, and highest SES quartile).

Residential Setting

Rural-urban commuting area (RUCA) codes were used to classify the residential setting corresponding to each recipient's zip code. A RUCA code is assigned to each U.S. zip code based on population density and employment commuting data. Rural-urban commuting area

classification takes into account that certain low population density suburban zip codes may be associated with more densely populated urban areas. The RUCA codes range from 1.0 (most urban) to 10.6 (most rural). Three RUCA categories were defined a priori: metropolitan (RUCA 1.0-3.9), micropolitan (RUCA 4.0-6.0), and rural (7.0-10.6).

Distance from Transplant Center

The distance between each recipient's residence and their transplant center was calculated using the latitude and longitude of the geographic centroid of the patient's zip code and the latitude and longitude of the transplant center ascertained by Google maps search. Zip code locations were obtained from the 'zip code' package available through R, which contains a database of latitudes and longitudes for US zip codes from the CivicSpace database (August 2004) and augmented with data from federalgovernmentzipcodes.us (Jan 22, 2012). To account for the curve of the earth, the distance in miles was calculated using an arc-distance equation with the latitudes and longitudes expressed in radians (acos(cos(lat1) × cos(lat2) + sin(lat1) × sin(lat2) × cos(long1-long2)) × 3958.756) (33). Distance categories were determined by empirical exploration of the data.

Statistical Analysis

We compared differences in baseline characteristics across community risk categories (lowest risk, low-intermediate risk, high-intermediate risk, highest risk) using one-way analysis of variance for continuous variables and chi-squared tests for categorical variables. We estimated the relative risk of EHR associated with each social determinant of health (community risk score, SES, residential setting, and distance to center) using modified Poisson regression (13). We checked for collinearity between the social determinants of health and the mean variance inflation factor was 1.38 (range 1.14-1.38), suggesting little to no collinearity. A single model was used which included each of the four social determinants of health (community risk score, SES,

residential setting, and distance to center), as well as the following recipient, donor, and transplant characteristics based on our previously published model of EHR: age, sex, race, BMI, history of comorbidity (hypertension, cancer, hepatitis C positive, chronic obstructive pulmonary disease, diabetes, current smoker, congestive heart failure, and dialysis vintage), donor age, donor type (standard criteria, extended criteria, donor after cardiac death), human leukocyte antigen (HLA) mismatch, use of induction therapy, and length of stay for KT admission (1). Socioeconomic status index was categorized by quartile. Based on empirical exploration of the data, distance was categorized as <10 miles, 10-90 miles, 90-180 miles, 180-240 miles, and >240 miles. A separate model, adjusted for recipient, donor, and transplant characteristics was used to estimate the relative risk of EHR associated with each component of the community risk score. Similarly a separate model, adjusted for recipient, donor, and transplant characteristics, was used to estimate the relative risk of EHR associated with each component of the SES index. Confidence intervals are reported as per the method of Louis and Zeger, as previously described (14, 15). All analyses were performed using STATA 14.0/MP for Linux (Stata Corp LP, College Station, TX, USA).

RESULTS

Study Population

There were 52,738 adult first-time KT recipients with available zip code and county code information. In univariate analyses recipients living within the highest risk communities were more likely to be African American, obese, and have a higher burden of comorbidity (hypertension, CMV, COPD, smoking, and congestive heart failure). Recipients living within the highest risk communities were also more likely to have a low SES and live in a rural setting (Table 2.1).

Community Risk

The mean community risk score was 15.3 (SD=9.0) (median 14, IQR 8-21). In multivariate analysis adjusted for recipient, donor, and transplant characteristics and adjusted for SES, residential setting, and distance from center there was an association between community risk and EHR. Living in a low-intermediate risk (aRR $_{1.04}1.07_{1.11}$, p<0.001), high-intermediate risk ($_{1.02}1.07_{1.11}$, p=0.002), or highest risk community ($_{1.04}1.10_{1.16}$, p=0.001) was associated with an increased risk of EHR (Table 2.2).

In multivariate analysis adjusted for recipient, donor, and transplant characteristics readmission was associated with several components of community risk. For every 10% increase in the county prevalence of smoking there was a 1.04-fold increase in the risk of readmission (aRR $_{1.01}1.04_{1.07}$, p=0.004) (Table 2.3). For every 100 preventable hospitalizations per county there was a 1.25-fold increase in the risk of EHR for the recipient (aRR $_{1.11}1.25_{1.33}$, p<0.001). For every 10% increase in the county prevalence of physical inactivity, there was a 1.07-fold increase in the risk of EHR (aRR $_{1.04}1.07_{1.10}$, p<0.001). For every 10% increase in county prevalence of adult obesity, there was a 1.04-fold increase in the risk of EHR (aRR $_{1.01}1.04_{1.07}$, p=0.02). For every 10% increase in the county prevalence of low birth weight there was a 1.09-fold increase in the risk of EHR (aRR $_{1.01}1.09_{1.19}$, p=0.03). However, there was no statistically significant association between median household income, poor physical health, poor mental health, poor/fair health, or potential life years lost and EHR.

Socioeconomic Status

The mean SES index was 58.6 (SD=7.6)(median 58.7, IQR 53.1 to 64.4). In multivariate analysis adjusted for recipient, donor, and transplant characteristics and adjusted for community risk, residential setting, and distance from center there was no statistically significant association between SES index and EHR (Table 2.2).

In multivariate analysis adjusted for recipient, donor, and transplant characteristics EHR was associated with one component of the SES index. For every 1% increase in the proportion of zip code crowding there was a 0.69-fold decrease in the risk of EHR (aRR $_{0.48}0.69_{0.99}$ p=0.048) (Table 2.4). However, there was no statistically significant association between median annual household income, property value, prevalence of poverty, prevalence of adults with a college education or higher, prevalence of adults with lower than a high school education, or prevalence of unemployment and EHR.

Residential Setting

Of patients studied, 82.2% lived in an urban area, 9.7% lived in a micropolitan area, and 8.1% lived in a rural area. The mean distance to center for urban recipients was 15.1 miles, compared to 72.2 miles for micropolitan and 84.4 miles for rural recipients. However, in multivariate analysis adjusted for recipient, donor, and transplant characteristics and adjusted for community risk, SES, and distance from center there was no statistically significant association between residential setting and EHR (Table 2.2).

Distance to Transplant Center

The mean distance from recipient home to transplant center was 44.9 miles (SD=52.4) (median 21.9, IQR 8.0-64.4), 30.5% lived less than 10 miles from their transplant center, 52.6% between 10 and 90 miles, 13.2% between 90 and 180 miles, 3.6% between 180 and 240 miles, and 0.3% greater than 240 miles from their transplant center. In multivariate analysis adjusted for recipient, donor, and transplant characteristics and adjusted for community risk, SES, and residential setting there was an inverse association between distance from center and risk of EHR. Compared to recipients living less than 10 miles away, there was a 0.97-fold decrease in the risk of readmission for those living 10 to 90 miles away (aRR $_{0.94}0.97_{0.99}$, p=0.03), a 0.90-fold decrease in the risk for

recipients living 90 to 180 miles away (aRR $_{0.86}0.90_{0.94}$, p<0.001), a 0.82-fold decrease in the risk for recipients living 180 to 240 miles away (aRR $_{0.76}0.82_{0.89}$, p<0.001), and a 0.94-fold decrease in risk for recipients living greater than 240 miles away (aOR $_{0.74}0.94_{1.21}$, p=0.6) (Table 2.2).

DISCUSSION

In this national registry study of 52,738 KT recipients, EHR was associated with certain social determinants of health. Increased community risk was associated with an increased risk of EHR, and was likely driven by the association between EHR and several components of community risk that capture health behaviors within a given county (preventable hospitalizations, prevalence of physical inactivity, prevalence of low birth weight, and prevalence of smoking). Early hospital readmission was not associated with SES or residential setting. Recipients that lived within ten miles of their transplant center had an increased risk of EHR compared to all other distance categories. However, the difference was smallest between those living less than 10 miles away and those living greater than 240 miles away, possibly because patients living greater than 240 miles from the transplant center temporarily stay in close proximity to the center immediately following transplant discharge.

Our study is the first to examine the association between community risk and EHR. Community risk has been shown to be associated with other post-transplant outcomes. Schold et al. found that KT recipients from the highest risk communities had a 1.50-fold increase in the risk of graft loss and a 1.45-fold increase in the risk of post-KT mortality (25, 26). Interestingly, we found an increased risk of EHR among recipients in all counties that were not lowest risk, compared to Schold's finding related to mortality wherein only recipients in the highest risk communities were at an elevated risk.

We found no association between SES index and EHR, which is consistent with previous work on readmission following KT. In a single center study of 753 KT recipients, Marhay et al. used the same SES index used in our study and found no association between SES and readmission (4). Interestingly, SES has been shown to be associated with other post-transplant outcomes. In particular, Axelrod et al. found an association between the SES index and post-KT mortality (27). Early hospital readmission, although associated with post-transplant survival, may be a mechanistically different outcome, which is independent of SES. Across other fields, the association between SES and readmission varies. In a systematic review of readmissions following hospitalization for community acquired pneumonia and heart failure, Cavillio-King et al. showed that readmission was associated with lower education, low income, and unemployment (34). In a study of 12,000 patients admitted to four large hospitals in Massachusetts, Weissman et al. showed that poor patients and unskilled laborers both had a 1.25-fold increase in the odds of readmission (35). Conversely, in a study of 13,338 orthopedic patients, Hunter et al. showed that after adjusting for other patient-level characteristics, median household income, ascertained through census data, was not associated with readmission (aOR $_{0.49}0.73_{1.09}$, high income compared to low income) (36).

We found no association between EHR and residential setting. Our findings are consistent with the largest longitudinal study of readmission and residential setting among Medicare beneficiaries. In a study 11,733 Medicare beneficiaries, Toth et al showed that after adjusting for patient-level characteristics rural residency was not associated with readmission (aOR $_{0.86}1.00_{1.17}$ for larger rural setting; aOR $_{0.97}1.20_{1.49}$ for small rural setting; aOR $_{0.95}1.17_{1.44}$ for isolated rural setting) (37).

We found that distance to transplant center was associated with EHR in a stepwise fashion. Recipients living within ten miles of their transplant center were at highest risk and in general that

risk decreased as distance increased. Across other fields, the association between readmission and distance varies. Similar to our findings, in a study of 10,633 cases of athroplasty, Zmistowski et al. showed that the risk of readmission decreased with increasing distance from the hospital (aOR $_{0.40}0.52_{0.66}$ per mile) (38). In a study of 148 patients undergoing placement of a left ventricular assist device, Hernandez et al. found that distance was associated with a decrease in the risk of readmission (aOR $_{0.995}0.998_{0.999}$ per mile) (39). Conversely, in a study of 23,779 patients undergoing major cancer surgery, Stitzenberg et al. found that compared to the closest quartile of distance, living in the second and fourth quartiles of distance increased the risk of readmission (second quartile: aIRR 1.27, fourth quartile: aIRR 1.14) (40).

Our study had several notable limitations. Our study population is limited to Medicare-primary KT recipients, who may be systematically different from KT recipients with private insurance. However, over half of all KT recipients are insured through Medicare and eligibility is determined based on their renal failure rather than traditional eligibility based on disability or age. Another limitation is that we were unable to ascertain community risk, SES, and distance at the patient-level. Instead we had to use surrogate measures based on patient county and zip code. Our analysis may miss important variation within county or within zip code. Variation may be common within large counties or zip codes. However, our findings are largely consistent with existing literature, some of which used more granular measures.

Social determinants of health, including health behaviors of the surrounding community and distance from transplant center, contribute significantly to EHR and must be considered to develop personalized post-KT care plans that aim at maximizing outcomes while minimizing complications and cost. By leveraging knowledge of a recipient's social situation following KT, providers may be able to avoid EHR and its long-term effects.

Table 2.1: Study population characteristics, by community risk score, n=52,738. County health rankings were used to generate a community risk score for each recipient's county of residence based on ten health indicators (median annual household income, prevalence of smoking, preventable hospitalizations, prevalence of physical activity, prevalence of adult obesity, prevalence of low birth weight, prevalence of poor physical health, prevalence of poor mental health, prevalence of poor/fair health, years of potential life lost). Table on next page.

	Lowest Community Risk (0-10)	Low-Intermediate Community Risk (11-20)	High-Intermediate Community Risk (21-30)	Highest Community Risk (31-40)	p-value
Recipients experiencing readmission, %	30.0	32.2	32.4	33.6	<0.001
Median age, IQR (years)	54, 42-64	53, 42-62	53, 42-62	52, 41-60	<0.001
Female, %	38.6	38.9	39.7	39.0	0.3
African American race, %	23.1	30.9	42.1	52.0	<0.001
Recipient BMI (kg/m2), %					<0.001
Underweight (<18.5)	2.4	2.1	2.0	2.0	
Normal (18.5-25)	33.8	32.4	28.6	30.2	
Overweight (25-30)	34.0	34.2	33.8	33.8	
Obese (>30)	30.0	31.3	35.6	34.0	
Hypertension, %	77.5	77.8	80.7	78.6	<0.001
Cancer, %	2.4	1.9	2.2	1.9	0.03
Hepatitis C positive, %	5.0	5.2	6.1	7.0	<0.001
Chronic obstructive pulmonary disease, %	1.7	1.7	2.4	2.0	<0.001
Diabetes, %	34.4	36.0	37.0	34.2	0.003
Current smoker, %	4.0	3.8	5.4	6.2	<0.001
Congestive heart failure	12.0	12.5	14.3	13.3	<0.001
Median dialysis vintage, IQR (years)	3.3, 1.7-4.9	3.4, 1.9-5.1	3.4, 1.8-5.0	3.2, 1.7-4.9	<0.001
Socioeconomic quartile, %					<0.001
1	7.2	22.3	42.6	69.8	
2	16.0	29.3	32.9	21.3	
3	28.7	28.8	18.2	6.9	
4	48.1	19.6	6.4	1.9	
Residential setting					<0.001
Urban	90.3	86.8	72.9	44.3	
Micropolitan	5.8	7.2	16.0	25.0	
Rural	3.9	6.0	11.0	30.6	
Distance from transplant center, %					<0.001
< 10 miles	24.5	32.6	29.6	25.9	
10 to 90 miles	49.5	48.8	42.4	44.3	
90 to 180 miles	7.2	8.4	15.4	19.9	
180 to 240 miles	1.5	3.8	3.7	3.4	
> 240 miles	7.4	6.5	8.8	6.9	

Table 2.2: Relative risk of early hospital readmission following kidney transplantation, by social determinants of heath. The relative risk of early hospital readmission for each social determinant of health (community risk, socioeconomic status, residential setting, and distance from transplant center) was estimated in a single multivariate model adjusted for recipient, donor, and transplant characteristics.

	aRR	p-value
Community risk score		
Lowest risk (0-10)	REF	-
Low-Intermediate risk (11-20)	$_{1.04}1.07_{1.11}$	<0.001
High-Intermediate risk (21-30)	$_{1.02}1.07_{1.11}$	0.002
Highest risk (31-20)	$_{1.04}1.10_{1.16}$	0.001
Socioeconomic index quartile		
Lowest SES quartile	$_{0.93}0.97_{1.01}$	0.2
Low-Intermediate SES quartile	$_{0.97}1.01_{1.05}$	0.6
High-Intermediate SES quartile	$_{0.94}0.97_{1.01}$	0.2
Highest SES quartile	REF	-
Residential Setting		
Urban	REF	-
Micropolitan	$_{0.92}0.96_{1.01}$	0.1
Rural	$_{0.95}1.01_{1.06}$	0.8
Distance from transplant center, miles		
<10	REF	-
10-90	$_{0.94}0.97_{0.99}$	0.03
90-180	$_{0.86}0.90_{0.94}$	<0.001
180-240	$_{0.76}0.82_{0.88}$	<0.001
>240	$_{0.74}0.94_{1.21}$	0.6

Adjusted for age, sex, race, body mass index, diabetes, hypertension, chronic obstructive pulmonary disease, congestive heart failure, cancer, smoking, hepatitis C seropositivity, donor type, donor age, receipt of induction therapy, zero HLA mismatch, transplant length of stay.

Table 2.3: Relative risk of early hospital readmission following kidney transplantation, by each component of the community risk score. Each component is at the county level and was explored in a separate model adjusted for recipient, donor, and transplant characteristics.

	aRR	p-value
Median annual household income, per $10,000	$_{0.90}0.99_{1.00}$	0.1
Prevalence of smoking, per 10% increase	$_{1.03}1.06_{1.09}$	<0.001
Preventable hospitalizations, per 10 hospitalizations	$_{1.02}1.02_{1.03}$	<0.001
Prevalence of physical inactivity, per 10% increase	$_{1.04}1.07_{1.10}$	<0.001
Prevalence of adult obesity, per 10% increase	$_{1.01}1.04_{1.07}$	0.02
Prevalence of low birth weight, per 10% increase	$_{1.01}1.09_{1.19}$	0.03
Prevalence of poor physical health, per 10% increase	$_{0.98}1.19_{1.46}$	0.08
Prevalence of poor mental health, per 10% increase	$_{0.95}1.17_{1.44}$	0.1
Prevalence of poor/fair health, per 10% increase	$_{0.96}0.99_{1.02}$	0.4
Years potential life lost, per 10 years	$_{0.99}1.00_{1.00}$	0.07

Adjusted for age, sex, race, body mass index, diabetes, hypertension, chronic obstructive pulmonary disease, congestive heart failure, cancer, smoking, hepatitis C seropositivity, donor type, donor age, receipt of induction therapy, zero HLA mismatch, transplant length of stay.

Table 2.4: Relative risk of early hospital readmission following kidney transplantation, by each component of the socioeconomic status index. Each component is at the zip code level and was explored in a separate adjusted model.

	aRR	p-value
Median annual household Income, per $10,000	$_{0.99}0.99_{1.00}$	0.7
Prevalence of crowding, per 1% increase	$_{0.48}0.69_{0.99}$	0.048
Prevalence of poverty, per 1% increase	$_{0.99}1.00_{1.00}$	0.7
Mean property value, per $10,000	$_{0.99}1.00_{1.00}$	0.4
Adults with college education or higher, per 1% increase	$_{0.99}1.00_{1.00}$	0.8
Adults with high school education or lower, per 1% increase	$_{0.99}0.99_{1.00}$	0.3
Prevalence of unemployment	$_{0.99}1.00_{1.00}$	0.4

Adjusted for age, sex, race, body mass index, diabetes, hypertension, chronic obstructive pulmonary disease, congestive heart failure, cancer, smoking, hepatitis C seropositivity, donor type, donor age, receipt of induction therapy, zero HLA mismatch, transplant length of stay.

CHAPTER 3: IMPACT OF READMISSION FOLLOWING KIDNEY TRANSPLANTATION

SUMMARY:

Following kidney transplantation, early readmission is independently associated with graft loss and mortality, but the mechanism of this association is poorly understood. A better understanding of the timeline of risk, i.e. during the readmission hospitalization versus time periods post-readmission, is needed to provide additional insights. We used national registry data to study 56,076 adult Medicare-primary first-time kidney transplant recipients from December 1999-October 2011. Piecewise Cox proportional hazard models were used to estimate the association between graft loss, mortality, and readmission for two time periods: readmission hospitalization and post-readmission. During the readmission hospitalization, graft loss was substantially higher (deceased donor hazard ratio: $_{19.3}25.2_{32.9}$, $p<0.001$; live donor: $_{18.1}36.7_{74.2}$, $p<0.001$) and mortality was substantially higher (deceased donor: $_{13.9}18.1_{23.4}$, $p<0.001$; live donor: $_{9.00}18.2_{41.3}$, $p<0.001$). Immediately following readmission discharge, graft loss (deceased donor: $_{2.19}2.44_{2.73}$, $p<0.001$; live donor: $_{2.00}2.50_{3.13}$, $p<0.001$) and mortality (deceased donor: $_{2.20}2.44_{2.71}$, $p<0.001$; live donor: $_{1.90}2.34_{2.88}$, $p<0.001$) remained elevated, but much less so. In the years following readmission, the hazard of graft loss remained, but further decreased 19% per year for deceased donor recipients (time varying coefficient $_{0.78}0.81_{0.85}$, $p<0.001$) and 14% per year for live donor recipients ($_{0.79}0.86_{0.93}$, $p<0.001$). The hazard of mortality remained, but further decreased 14% per year for deceased donor recipients ($_{0.83}0.86_{0.89}$, $p<0.001$) and 9% per year for live donor recipients($_{0.85}0.91_{0.98}$, $p<0.001$). In conclusion, readmission is most strongly associated with graft loss and mortality during the readmission hospitalization, but also portends a lasting, albeit attenuated, risk post-readmission.

INTRODUCTION

Over 30% of kidney transplant (KT) recipients experience early hospital readmission (EHR), or re-hospitalization within 30 days of discharge following KT (1). To appropriately manage these recipients, it is vital to understand the immediate and long-term ramifications of EHR. Early hospital readmission increases the risk of subsequent hospitalization within the first year following KT. In addition, EHR is associated with inferior graft and patient survival. Deceased donor KT recipients who experience EHR are 1.43 times more likely to lose their graft and 1.50 times more likely to die compared to recipients who do not experience EHR. The same is true among live donor KT recipients who experience EHR; with a 1.54 fold increase in graft loss and a 1.45 fold increase in mortality (2).

Existing estimates of the association between graft loss, mortality, and EHR, may be misleading. These numbers suggest that upon readmission to the hospital, a recipient's risk for graft loss increases by approximately 50% and their risk remains elevated indefinitely after the readmission is over. In other words, the risk of graft loss and death for recipients who are acutely ill and readmitted to the hospital is considered the same as the risk for recipients who experienced EHR in the past, survived that readmission, and are currently months or years post-readmission. Prior work in transplantation, and other fields, assumes that the risk associated with EHR is constant over time without considering the possibility that it may vary with time (2, 41-49). In particular, the association between EHR and adverse transplant outcomes may be substantially different for KT recipients that are in the hospital experiencing EHR and those that have previously experienced EHR. Furthermore, it is unknown whether recipients who previously experienced EHR carry an increased risk of adverse outcomes for the remainder of their life or if that risk attenuates over time. Assuming a constant association may underestimate the risk attributable to the readmission hospitalization and it may give an inaccurate estimate of the durability of that risk for recipients surviving post-readmission.

The objective of this study was to quantify the association between EHR and survival during two distinct time periods: the EHR hospitalization and post-EHR. A second objective of the study was to determine whether the association between EHR and survival is constant during post-EHR follow-up.

METHODS

Study Population

The study population included 56,076 adult first-time KT recipients from December 1, 1999 through October 31, 2011 who had Medicare Part A and B as their primary insurance for at least 60 days before and 60 days following the date of transplant. Recipient, donor, and transplant characteristics were obtained from Organ Procurement Transplantation Network data. This study was reviewed by the institutional review board at Johns Hopkins School of Medicine and determined to qualify for an exemption under 45 CFR 46.101(b) as study participants cannot be identified directly or through linked identifiers.

Exposure and Outcome Ascertainment

EHR hospitalization was captured using United States Renal Data System (USRDS) claims data. As specified in our previously published models of EHR following KT, EHR was defined as any hospitalization to an acute care facility within 30 days of discharge after initial KT hospitalization (1, 2). KT recipients who died prior to initial discharge following KT were excluded (n= 1,743). KT recipients who had graft loss prior to discharge, but did not die, were also excluded from the analysis (n=1,489) because readmission in a recipient with a functioning graft at the time of discharge is mechanistically different than readmission of a recipient who has already lost their graft.

Association Between EHR and Survival

Cox proportional hazard models were used to estimate the hazard of death-censored graft loss and mortality associated with EHR. Separate models were used for deceased donor kidney transplant (DDKT) and live donor kidney transplant (LDKT). Each model was adjusted for recipient, donor, and transplant characteristics based on the Scientific Registry of Transplant Recipients risk adjustment models (50). Models for DDKT were adjusted for age, sex, African American race, body mass index (BMI), pre-emptive transplant, cause of end stage renal disease (ESRD), peak panel reactive antibody, hepatitis C status, time on dialysis, human leukocyte antigen (HLA) mismatch, pulsatile perfusion, cold ischemic time, donor/recipient weight ratio, donor race, terminal creatinine, donor hypertension, donor diabetes, extended criteria donor, donation after cardiac death, regional/national sharing. Models for LDKT were adjusted for age sex, African American race, BMI, pre-emptive transplant, cause of ESRD, peak panel reactive antibody, hepatitis C status, time on dialysis, HLA mismatch, recipient/donor weight ratio, donor race. Recipients were censored at 5 years of follow-up, time of re-transplant, or administratively at end-of-study. We used a clustered sandwich estimator for standard errors to account for possible center-level correlation. The proportional hazard assumption for each model was confirmed visually using log-log plots and Schoenfeld residuals.

We estimated the hazard of death-censored graft loss and mortality for two distinct time periods: from EHR admission date to EHR discharge or death/graft loss (EHR hospitalization) and from EHR discharge date to death/graft loss or censorship (post-EHR). To avoid immortal person-time bias among KT recipients with EHR (requiring patient and graft survival up to the point of readmission) we used a standard method of late entries in which the recipients with EHR only contributed to the exposed risk set starting at the time of admission for the EHR hospitalization. Based on exploratory data analysis and prior hypotheses, the attributable hazard during the EHR hospitalization was treated as constant and we used a time-varying coefficient to estimate

attributable hazard during the post-EHR time period. In other words, the estimate for "EHR hospitalization" represents the hazard averaged over the entire hospitalization while the "post-EHR" hazard represents the hazard at the time of EHR discharge and that hazard can vary based on the amount of time since EHR discharge.

Statistical Analysis

Confidence intervals are reported as per the method of Louis and Zeger, as previously described (14, 15). All analyses were performed using STATA 14.0/MP for Linux (Stata Corp LP, College Station, TX, USA).

RESULTS

Early Hospital Readmission

Of 56,076 KT recipients, 17,739 experienced EHR (31.6%) (Table 3.1). The median time from transplant discharge to EHR was 8 days (IQR 4-15). Among recipients who experienced EHR, the length of stay for the EHR hospitalization ranged from 1 to 217 days with a median length of stay of 4 days (IQR 2-7 days).

Crude Death-censored Graft Loss and Mortality

Crude death-censored graft loss within 30 days of transplant discharge was 1.5% for recipients who experienced EHR and 0.2% for recipients without EHR ($p<0.001$). Crude mortality within 30 days of transplant discharge was 0.8% for recipients who experienced EHR and 0.2% for recipients without EHR ($p<0.001$). Crude death-censored graft loss within one year of transplant discharge was 7.2% for recipients who experienced EHR and 2.4% for recipients without EHR ($p<0.001$). Crude mortality within one year of transplant discharge was 7.3% for recipients who experienced EHR and 2.5% for recipients without EHR ($p<0.001$).

Association Between EHR and Survival During the EHR Hospitalization Time Period

During the EHR hospitalization, 1.2% (n=218) of recipients lost their graft. Median time from EHR admission to death-censored graft loss was 4 days (IQR 1-14), with 48 recipients losing their graft on the same day as EHR admission. During the EHR hospitalization, 0.9% (n=158) of recipients died. Median time from EHR admission to death was 12 days (IQR 3-29), with 11 recipients dying on the same day as EHR admission. In an adjusted model, during the EHR hospitalization, DDKT recipients who experienced EHR were 25.2-times more likely to lose their graft compared to recipients without EHR (aHR $_{19.3}25.2_{32.9}$, p<0.001) (Table 3.2). LDKT recipients who experienced EHR were 36.7-times more likely to lose their graft compared to recipients without EHR (aHR $_{18.1}36.7_{74.2}$, p<0.001). During the EHR hospitalization, DDKT recipients who experienced EHR were 18.1-times more likely to die compared to recipients without EHR (aHR $_{13.9}18.1_{23.4}$, p<0.001). LDKT recipients who experienced EHR were 18.2-times more likely to die compared to recipients without EHR (aHR $_{9.00}18.2_{41.3}$, p<0.001).

Association Between EHR and Survival During the Post-EHR Time Period

During the post-EHR time period, 33.6% (n=5845) of recipients lost their graft, with a median time from EHR discharge to death-censored graft loss of 687 days (IQR 238-1212) and 355 recipients losing their graft within 30 days of EHR discharge. During the post-EHR time period, 22.5% (n=3953) of recipients died, with a median time from EHR discharge to death of 766 days (IQR 277-1265) and 158 recipients dying within 30 days of EHR discharge. In an adjusted model, during the post-EHR time period, DDKT recipients who previously experienced EHR were 2.44-times more likely to lose their graft compared to recipients without EHR (aHR $_{2.19}2.44_{2.73}$, p<0.001) (Table 3.2). LDKT recipients who previously experienced EHR were 2.50-times more likely to lose their graft compared to recipients without EHR (aHR $_{2.00}2.50_{3.13}$,p<0.001). During the post-EHR time period, DDKT recipients who previously experienced EHR were 2.44-times more likely to die compared to recipient without EHR (aHR $_{2.20}2.44_{2.71}$, p<0.001). LDKT

recipients who previously experienced EHR were at a 2.34-times more likely to die compared to recipients without EHR (aHR $_{1.90}2.34_{2.88}$, p<0.001). During the post-EHR time period, the hazard of graft loss for recipients who previously experienced EHR decreased linearly over time by 19% per year for DDKT recipients (time varying coefficient (tvc) $_{0.78}0.81_{0.85}$, p<0.001) (Figure 3.1A) and 14% per year for LDKT recipients (tvc $_{0.79}0.86_{0.93}$, p<0.001) (Figure 3.1B). During the post-EHR time period, the hazard of death for recipients who previously experienced EHR decreased linearly over time by 14% per year for DDKT recipients (tvc $_{0.83}0.86_{0.89}$, p<0.001) (Figure 3.2A) and by 9% per year for LDKT recipients (tvc $_{0.85}0.91_{0.98}$, p=0.009) (Figure 3.2B).

DISCUSSION

In this national study of 56,076 first-time KT recipients, we found that the association between EHR and adverse transplant outcomes is dynamic. The majority of death-censored graft loss and mortality attributable to EHR occurred during the EHR hospitalization. During the EHR hospitalization, graft loss was 25.2-times higher for DDKT recipients and 36.7-times higher for LDKT recipients. Similarly, mortality was 18.1-times higher for DDKT recipients and 18.2-times higher for LDKT recipients. Immediately following readmission discharge, graft loss and mortality remained elevated, but much less so. Graft loss was 2.44-times higher for DDKT recipients and 2.50-times higher for LDKT recipients. Similarly, mortality was 2.44-times higher for DDKT recipients and 2.34-times higher for LDKT recipients. The hazard of death-censored graft loss and mortality continued to decrease with long-term post-EHR follow-up.

Current understanding of the association between EHR and mortality averages the risk attributable to EHR over the entire follow-up period. This approach may underestimate the risk during readmission hospitalization and may over-estimate the risk post-readmission. In our previous work on EHR following KT, we found that EHR was associated with 1.50-times higher mortality over 5 years of follow-up (2). Our new approach demonstrates that the risk attributable

to EHR is highest during the EHR hospitalization and declines over time. Outside the field of transplantation, readmission is a well-understood risk factor for mortality following surgery. Following various surgical procedures, including pancreatectomy, coronary artery bypass grafting, orthopedic repairs, colectomy, esophagectomy, and lung cancer resection, EHR is associated with a 2.3 to 6.6-fold increase in the risk of mortality (2, 41, 42, 46-49, 51). Interestingly, studies with longer follow-up have a lower estimated risk ratio, indicating the effect may be a partial artifact of study design and follow-up time.

Our study is not the first to use time-varying exposure methods to change the understanding of a biological process (52-55). Previous work by our group used similar methods to show that in pediatric KT recipients and liver transplant recipients the hazard of graft loss varies over time and is highest during late adolescence and early adulthood (52, 53). Beyond the field of transplantation, several studies have used these methods. Bolard et al. used piecewise Cox proportional hazard models to show that the hazard of mortality by cancer stage varied with time post diagnosis (54). Similarly, Platt et al. used extended Cox proportional hazard models with time-varying covariates to better characterize predictors of fetal and infant mortality over the timeline of gestation (55). Our study is novel in treating EHR as a time-varying risk factor for adverse post-KT outcomes and to our knowledge is the first study to use these methods in the context of studying readmission.

Our findings may have practical implications for management of KT recipients experiencing EHR. EHR substantially increases the risk during the EHR hospitalization. Recipients experiencing EHR should be managed with caution. Following EHR discharge, the risk of graft loss and mortality is attenuated but does not disappear completely. Detailed discharge planning, frequent outpatient follow-up, and open communication between the recipient and transplant team may help mitigate the risk immediately post-EHR. Conversely, several years post-EHR, the

remaining risk is minimal and recipients that make it to this point are unlikely to require specialized care.

Our study had several notable limitations. To ascertain readmission we had to limit our study population to with Medicare as their primary insurer. Medicare primary KT-recipients may be systematically different than KT recipients with alternative insurance providers. However, Medicare is the leading primary insurer for approximately half of all KT recipients, making our study population an important sub-set of the general KT population. In addition, since all individuals with end-stage renal disease (ESRD) requiring dialysis are Medicare eligible, regardless of age or disability, our inferences should be minimally affected. A further limitation of our study is that we cannot determine whether recipients that lost their graft during readmission were readmitted because they were already losing their graft or they lost their graft as a result of readmission. Similarly, death during readmission could represent failure to rescue or death due to the readmission itself. Even though we cannot directly delineate the casual pathway between EHR and adverse outcomes, our study is the first to isolate the EHR hospitalization time period as a source of substantial risk.

In conclusion, EHR remains a frequent and noteworthy occurrence post-KT. Recipients experiencing EHR should be managed with great care, as they are more susceptible to adverse outcomes both during the EHR hospitalization and for an extended period post-EHR.

Table 3.1: Study population characteristics, by early hospital readmission, n=56,076.

	No Early Hospital Readmissions n= 38,337	Early Hospital Readmissions n= 17,739	p-value
Median age, IQR (years)	53, 41-62	55, 44-63	< 0.001
Female (%)	38.9	39.3	0.3
African American race (%)	30.7	35.9	< 0.001
Recipient BMI, kg/m2 (%)			< 0.001
Underweight (<18.5)	2.2	2.1	
Normal (18.5-25)	32.5	29.9	
Overweight (25-30)	34.6	33.5	
Obese (>30)	30.8	34.4	
Hepatitis C positive (%)	4.9	6.6	<0.001
Cause of ESRD (%)			<0.001
Congenital	29.1	35.5	
Diabetes	26.3	25.1	
Glomerulonephritis	23.2	20.0	
Hypertension	7.3	5.9	
Unknown	13.9	13.4	
Median dialysis vintage, IQR (years)	3.3, 1.8-5.0	3.6, 2.0-5.4	<0.001
Median peak PRA, IQR	1, 0-16	2, 0-19	<0.001
Donor race			<0.001
Caucasian	66.9	67.5	
African American	14.0	16.0	
Other	19.1	16.5	
Donor recipient weight ratio	0.97, 0.77-1.2	0.95, 0.7-1.2	<0.001
Donor hypertension (%)	19.6	23.7	<0.001
Donor diabetes (%)	4.6	5.6	<0.001
Median donor creatinine, IQR (mg/dL)	1.0, 0.7-1.3	1.0, 0.7-1.3	0.003
Live donor (%)	24.2	21.1	<0.001
ECD donor (%)	13.5	17.6	<0.001
DCD donor (%)	6.9	8.0	<0.001
Pre-emptive kidney transplant (%)	2.6	2.6	0.9
HLA mismatch (%)			<0.001
0	7.9	6.3	
1	3.4	2.9	
2	7.9	6.7	
3	16.7	16.1	
4	22.9	22.9	
5	26.9	28.9	
6	14.2	16.2	
Regional/national share (%)	43.5	41.6	<0.001
Median cold ischemia time	15, 7.5-21.5	15.5, 8.5-22	<0.001
Pulsatile perfusion (%)	8.2	9.0	0.001

Table 3.2: Hazard of death-censored graft loss and mortality during early hospital readmission hospitalization (readmission hospitalization) and following early hospital readmission discharge (post-readmission).

	Readmission Hospitalization Graft Loss	Readmission Hospitalization Mortality	Post-Readmission Graft Loss	Post-Readmission Mortality
Deceased Donor Recipients[1]	$_{19.3}25.2_{32.9}$	$_{13.9}18.1_{23.4}$	$_{2.19}2.44_{2.73}$	$_{2.20}2.44_{2.71}$
Living Donor Recipients[2]	$_{18.1}36.7_{74.2}$	$_{9.00}18.2_{41.3}$	$_{2.00}2.50_{3.13}$	$_{1.90}2.34_{2.88}$

All p-values < 0.001

[1] Models adjusted for age, sex, African American race, body mass index, pre-emptive transplant, cause of end stage renal disease, peak panel reactive antibody, hepatitis C status, time on dialysis, human leukocyte antigen mismatch, pulsatile perfusion, cold ischemic time, donor/recipient weight ratio, donor race, terminal creatinine, donor hypertension, donor diabetes, extended criteria donor, donation after cardiac death, regional/national sharing.

[2] Models adjusted for age sex, African American race, body mass index, pre-emptive transplant, cause of end stage renal disease, peak panel reactive antibody, hepatitis C status, time on dialysis, human leukocyte antigen mismatch, recipient/donor weight ratio, donor race.

Figure 3.1: Hazard ratio of post-readmission death-censored graft loss over time, comparing readmitted to non-readmitted (reference) (A) deceased donor (DDKT) and (B) live donor (LDKT) kidney transplant recipients.

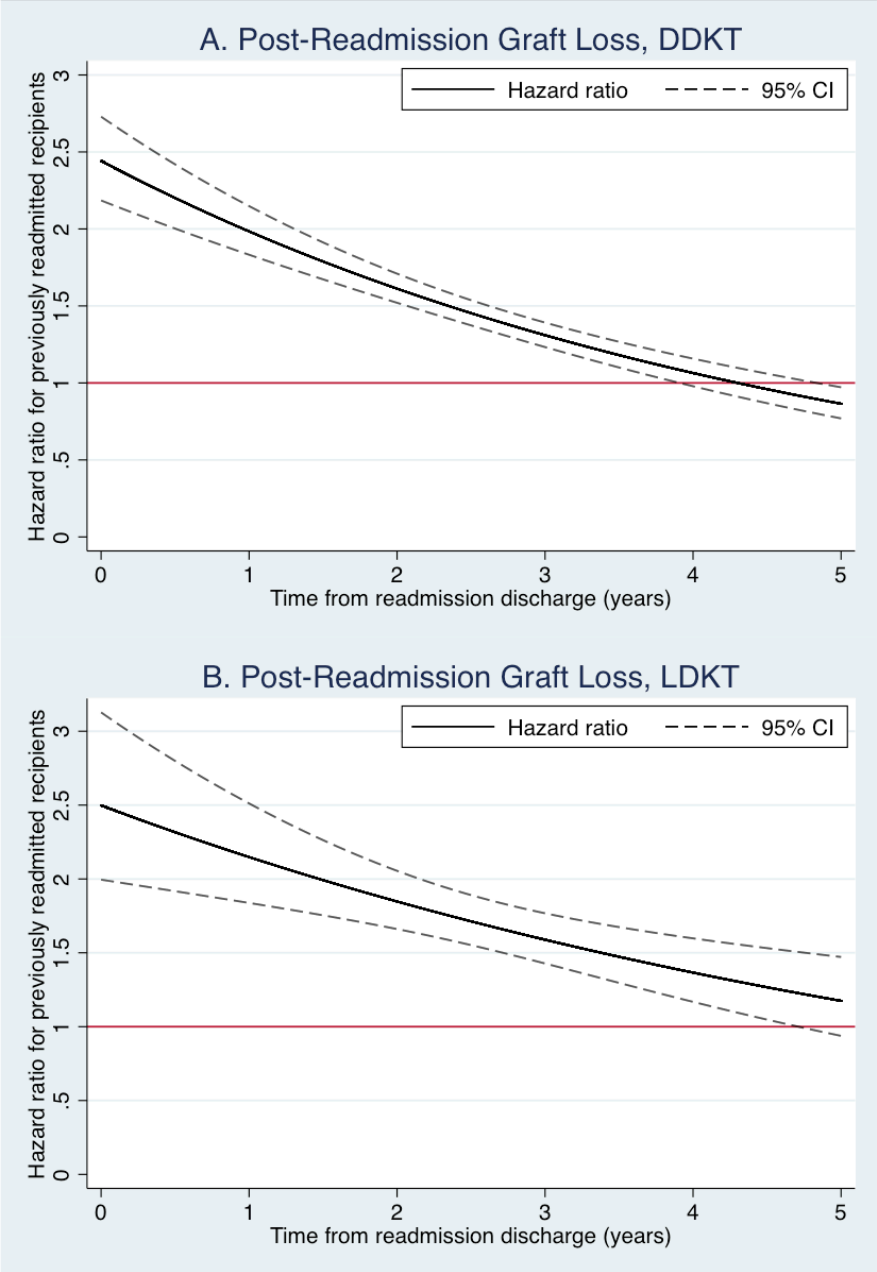
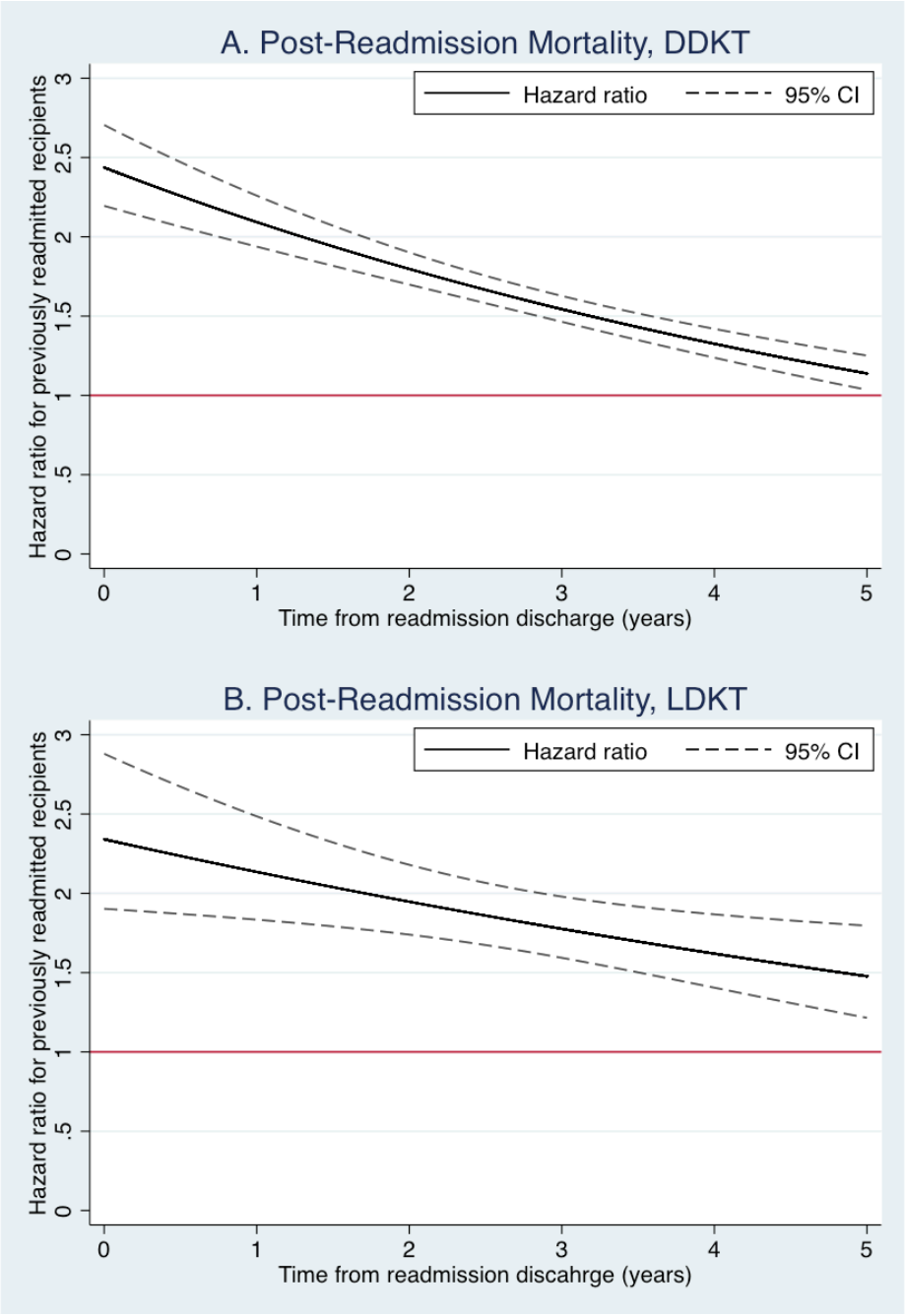


Figure 3.2: Hazard ratio of post-readmission mortality over time, comparing readmitted to non-readmitted (reference) (A) deceased donor (DDKT) and (B) live donor (LDKT) kidney transplant recipients.



CHAPTER 4: READMISSION FOLLOWING SIMULTANEOUS PANCREAS KIDNEY TRANSPLANTATION

SUMMARY:

Early hospital readmission is associated with increased morbidity, mortality, and cost. Following simultaneous pancreas-kidney transplantation, rates of readmission and risk factors for readmission are unknown. We used United States Renal Data System and Organ Procurement and Transplantation Network data to study 3,643 adult Medicare primary first-time simultaneous pancreas-kidney recipients from December 1, 1999 - October 31, 2011. Early hospital readmission was any hospitalization within 30 days of discharge. Modified Poisson regression was used to determine the association between readmission and patient-level factors. Empirical Bayes statistics were used to determine the variation attributable to center-level factors. The incidence of readmission was 55.5%. Each decade increase in age was associated with an 11% lower risk of readmission to age 40, beyond which there was no association. Donor African-American race was associated with a 13% higher risk of readmission. Each day increase in length of stay was associated with a 2% higher risk of readmission until 14 days, beyond which each day increase was associated with a 1% reduction in the risk of readmission. Center-level factors were not associated with readmission. The high incidence of early hospital readmission following simultaneous pancreas-kidney transplant may reflect clinical complexity rather than poor quality of care.

INTRODUCTION

Hospital readmission is associated with increased morbidity, mortality and cost among patients in the United States. Approximately 20% of all Medicare patients are readmitted to the hospital within 30 days of hospital discharge. Readmission results in potentially avoidable costs as high as $12 billion annually (56). Since passage of the Affordable Care Act, rates of readmission are increasingly used as a measure of hospital quality (57). In 2009 the Centers for Medicare and Medicaid (CMS) began publicly reporting hospital readmission rates for pneumonia, heart attack, and heart failure, and in fiscal year 2013 they began the Hospital Readmission Reduction Program (HRPR), which financially penalizes hospitals with excess Medicare readmissions. In the first year alone, the HRPR resulted in penalties totaling $280 million. The clinical and financial impact has led to significant effort toward preventing early hospital readmissions (EHR) (58).

General surgical readmissions have been well characterized. EHR in surgical patients has been associated with length of stay, comorbidities, and surgical complications. Rates of EHR following general surgery are as high as 22%, varying by center and procedure (30, 59-66). However, the frequency and patterns of readmission among transplant patients might differ greatly from those of general surgical patients because of the increased complexity of immunosuppression regimens, rejection, infection, and other transplant-specific complications. Based on national data, we recently demonstrated that 31% of kidney transplant recipients are readmitted within 30 days of discharge. We also identified a number of factors associated with EHR after kidney transplantation, including older age, African American race, various comorbidities (obesity, hypertension, diabetes, heart disease, chronic obstructive pulmonary disease, hepatitis C positive, and time on dialysis), expanded criteria donor, length of stay, lack of induction therapy, and frailty, a novel measure of physiologic reserve (1, 5).

Unlike our understanding of EHR among patients following kidney transplantation, little is known about EHR following simultaneous pancreas-kidney transplantation (SPK). SPK is an important treatment option for patients with diabetes and end stage renal disease, however it is substantially more complex than kidney transplantation alone (KTA). Technical failure rates following pancreas transplant are as high as 8%. Reasons for failure include graft thrombosis, graft pancreatitis, anastomotic leak, and infection (67, 68). SPK recipients require increased immunosuppression and are at risk for developing metabolic derangement and hyperglycemia as their pancreas allograft begins to function (69-74). Existing long-term sequelae of diabetes, like gastroparesis, neurogenic bladder, and autonomic neuropathy, can compound complications post-transplant (75-77). Given the high risk of perioperative complications, SPK recipients, on average, remain in the hospital longer than their KTA counterparts and have a higher risk of perioperative mortality (68, 69, 76-78). We hypothesize that the high-risk perioperative period following SPK is associated with increased EHR. However, the national landscape of EHR following SPK has not been described and risk factors for EHR are largely unknown. Two single center studies, of 98 and 93 SPK recipients, both demonstrate a readmission rate of approximately 74% within the first three months after transplant (78, 79). Although, these studies begin to quantify the burden of EHR following SPK they do not identify which patients are at risk for EHR. In addition, these studies are limited by a small sample size and poor generalizability of single center data. To better understand EHR in SPK, we used United States Renal Data System (USRDS) and Organ Procurement and Transplantation Network (OPTN) data to capture readmissions among Medicare beneficiaries undergoing SPK. The objectives of this study were to identify factors associated with EHR after SPK and to explore center-level heterogeneity in EHR across the United States.

MATERIALS AND METHODS

Study Population and EHR Ascertainment

The study population included 3,643 adult first-time SPK recipients from December 1, 1999 through October 31, 2011 who had Medicare Part A and B as their primary insurance for at least 60 days before and 60 days following the date of transplant. As specified in our previously published model of EHR following KTA, EHR was defined as at least one hospital readmission to any acute care hospital within 30 days of discharge after initial SPK hospitalization (1). Time to readmission is defined as the number of days from the date of SPK hospitalization discharge to the date of admission for the readmission hospitalization. SPK recipients that died prior to discharge were excluded (n= 101). SPK recipients that died within the first 30 days after SPK were excluded (n=72), unless EHR occurred prior to death (n=14). Donor, recipient, and transplant factors were obtained from national registry data. The reason for EHR was ascertained by diagnosis related group (DRG) code from USRDS claims data. Mortality information was augmented by linkage to the Social Security Death Master File and to CMS data. This study was reviewed by the institutional review board at Johns Hopkins School of Medicine and determined to qualify for an exemption under 45 CFR 46.101(b) as study participants cannot be identified directly or through linked identifiers.

Potential Factors Associated with EHR

The following recipient, donor, and transplant factors were explored for potential association with EHR: age, sex, race, BMI, history of comorbidity (hypertension, cancer, hepatitis C positive, chronic obstructive pulmonary disease, type 1 diabetes, current smoker, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and dialysis vintage), donor age, donor gender, donor race, donor height, donor BMI, donor type (standard criteria, extended criteria, donor after cardiac death), donor cause of death, cold ischemia time, terminal creatinine, human leukocyte antigen (HLA) mismatch, use of induction therapy, delayed graft function, method of

exocrine drainage, length of stay for SPK admission, and year of transplant. These factors were chosen based on our previously published model of EHR following KTA, the SRTR risk models for SPK, and empirical exploration (1, 50).

Center-level Factors Associated with EHR

The following center-level factors were explored for potential association with EHR: total SPK volume, average length of stay, percent of SPK recipients who were African American, median time to transplant, and percent preemptive transplants. Each center-level factor was calculated from OPTN data. We also explored the association between readmission following SPK and readmission following KTA by determining the observed to expected readmission ratio using empirical Bayes estimation and correlating at the center-level.

Statistical Analysis

We estimated the relative risk of EHR by patient-level factors using modified Poisson regression (13). The functional form for each continuous variable was informed by previous studies and ultimately determined empirically. The final multivariate model was selected for parsimony by minimizing the Akaike Information Criteria (AIC). Center-level heterogeneity and associated factors were explored using a random intercept, hierarchical (multilevel) model adjusted for important patient-level factors as determined above. All analyses were performed using STATA 13.0/MP for Linux (College Station, TX, USA).

RESULTS

EHR Incidence

Of the 3,643 SPK recipients studied, 2,021 (55.5%) experienced at least one readmission within 30 days of discharge after initial SPK hospitalization (Table 4.1). Mean and median time to EHR

was 8.8 (SD 7.4) and 7 (IQR 3-13) days (Figure 1). Mean and median length of stay for the EHR hospitalization was 7.3 (SD 9.7) and 4 (IQR 2-9) days.

Reason for EHR

Overall, the five most frequent primary reasons for EHR were infection (23.1%) , kidney/urinary tract disorders (16.2%), alimentary tract disorders (15.6%), pancreatic/hepatobiliary disorders (11.1), and electrolyte/nutritional disorders (10.3) (Table 4.2). Of all readmissions, 82.6% required medical management, 16.4% required surgical or procedural management, and management was unknown for 1%. The median length of the readmission varied by management type. The median length of stay was longer for readmissions requiring surgical or procedural management (11 days, IQR 6-18) compared to medical management (4 days, IQR 2-7).

Among patients with a readmission length of stay of 48 hours or less, or a short-stay readmission, the top five most frequent reasons for EHR were alimentary tract disorders (19.4%), electrolyte/nutritional disorders (19.4%), infection (16.4%), kidney/urinary tract disorders (15.8%), and pancreatic/hepatobiliary disorders (6.5%). Among short-stay readmissions, 96.9% required medical management, 2.1% required surgical or procedural management, and management was unknown for 1%.

Recipient Factors Associated with EHR

Recipient age was associated with EHR (Table 4.3). For every decade increase in age there was a 11% lower risk of EHR for recipients up to age 40 (aRR 0.89 per decade, 95% CI: 0.82-0.97, p=0.005). For example, a 40-year-old recipient would have a 21% lower risk of EHR than an 18-year-old recipient (aRR 0.77, 95% CI: 0.64-0.92, p=0.005). For recipients over age 40 there was no association between age and EHR (aRR 1.05 per decade, 95% CI: 0.97-1.15, p=0.2). There was no evidence of a statistically significant association between EHR and African American

recipient race, BMI, or history of peripheral vascular disease (Table 4.3). In preliminary models, there was no evidence of a statically significant association between EHR and recipient history of hypertension, cancer, hepatitis C, chronic obstructive pulmonary disease, type 1 diabetes, current smoker, congestive heart failure, cerebrovascular disease, dialysis vintage, or delayed graft function. These factors were excluded from the final model.

Donor Factors Associated with EHR

African American donor race and donor BMI were associated with EHR (Table 4.3). African American donor race was associated with a 13% higher risk of EHR (aRR 1.13 ,95% CI: 1.04-1.23, p=0.005). Overweight SPK recipients had a 12% higher risk of EHR compared to normal weight SPK recipients (aRR 1.12, 95% CI: 1.04-1.22, p=0.004). There was no evidence of a statistically significant association between EHR and an underweight BMI or obesity. In preliminary models, there was no evidence of a statistically significant association between EHR and donor age, donor gender, donor height, donor cause of death, extended criteria donor, donation after cardiac death, or terminal creatinine >2.5mg/dL (Table 4.3). These factors were excluded from the final model.

Transplant Factors Associated with EHR

The only transplant factor associated with EHR was length of stay for the initial SPK hospitalization (Table 4.3). Across the study population, length of stay ranged from 2 to 435 days; however, 93% of recipients had a length of stay between 5 and 30 days. Each increasing day of hospitalization was associated with a 2% increase risk of EHR up until 14 days (aRR 1.02 per day, 95% CI: 1.01-1.04, p<0.001), such that a length of stay of 14 days was associated with a 24% higher risk of EHR compared to a length of stay of 5 days (aRR 1.24, 95% CI: 1.13-1.37, p<0.001). After 14 days, each increasing day of hospitalization was associated with a 1% *decreased* risk of EHR (aRR 0.99 per day, 95% CI: 0.98-0.99, p<0.001), such that a length of

stay of 30 days was associated with a 14% *lower* risk of EHR compared to a length of stay of 14 days (aRR 0.86, 95%CI: 0.80-0.92, p<0.001), and no difference in risk of EHR compared to a length of stay of 5 days (aRR 1.07, 95% CI: 0.98-1.17, p=0.2). There was no evidence of a statically significant association between EHR and use of induction therapy (Table 4.3). In preliminary models, there was no evidence of a statistically significant association between EHR and cold ischemia time, HLA mismatch, method of exocrine drainage, or year of transplant. These factors were excluded from the final model.

Center-level Heterogeneity

The unadjusted rate of EHR by center ranged from 0% to 100%. After adjusting for patient-level factors (as delineated above), the ratio of observed to expected EHR varied by center from 0 to 1.88 (mean 1.00, SD 0.26, median 1.00, IQR 0.87-1.13) (Figure 4.1). No center-level factors (total SPK volume, average length of stay, percent of African American SPK recipients, median time to transplant, or percent preemptive transplants) were associated with EHR after adjustment for patient-level factors (Table 4.4). Including transplant center in a multilevel model improved the fit and a likelihood ratio test yielded a p-value < 0.001. However, the interclass correlation coefficient was 0.014 (SD 0.006), meaning only 1.4% of the variation was at the center-level. After adjustment for patient-level risk factors, only one center had a statistically significantly different incidence of EHR than the national average (Figure 4.2). Almost no correlation was found between the observed to expected ratio of readmission for SPK and KTA within transplant centers (correlation coefficient 0.1).

DISCUSSION

In this national database study of readmission after SPK, 55.5% of first-time Medicare-primary adult SPK recipients were readmitted within 30 days of discharge following transplantation. The most common reason for readmission was infection. Only 16.4% of EHR was managed by

surgical or procedural interventions. We identified several patient-level risk factors associated with EHR. Readmission was more likely to occur if recipients were younger, donor race was African American, or the donor was overweight. Length of stay following transplantation was associated with an increased risk of readmission to a threshold of 14 days, after which point the increased length of stay was protective against EHR. Center-level factors were not associated with EHR. In fact, center-level characteristics had almost no effect on the variation in EHR and the incidence of EHR was nearly constant across transplant centers.

Our findings provide a point of comparison between post-SPK and post-KTA readmissions. Overall, readmission is more prevalent following SPK (single center studies). In our previous study of 32,961 Medicare primary adult first-time KTA recipients, the incidence of EHR was 31% (1). The higher incidence of EHR following SPK is likely given that SPK is a longer, more technically challenging operation than KTA. In addition, SPK recipients are at high risk for rejection, infection, dehydration, and metabolic derangements (67, 68, 70, 71, 76, 78-80). Perioperative complications following SPK may necessitate readmission.

In our study, the most common reason for EHR was infection, accounting for 23.1% of readmissions. In our previous study of KTA, the most common reason for EHR was kidney/urinary tract disorders, accounting for 36% of readmissions, while infection only accounted for 12% of all post-KTA readmissions (1). For immunosuppressed, diabetic patients, it may be safer and ultimately beneficial to treat infections in the hospital, under direct monitoring. Collectively, kidney/urinary tract disorders and pancreatic/hepatobiliary disorders accounted for an additional 27.3% of post-SPK EHR. These readmissions are assumed to be secondary to complications with the respective allograft. Readmission in this setting may mitigate the development of more serious and costly complications later in the post-transplant course. In our study, 16.4% of all readmissions were managed by surgical or procedural interventions. Although

this is a relatively small proportion of total EHR, these readmissions may represent further examples of necessary and beneficial hospitalizations.

Among all readmissions, 26% were short-stays, meaning the readmission hospitalization lasted 48 hours or less. For short-stay readmissions, there is no point of comparison in the KTA literature. We would expect that short-stay readmissions be of lower acuity than prolonged readmissions. In our study, the most common reason for short-stay EHR was alimentary tract disorder or electrolyte/nutritional disorder, each accounting for 19.6% of readmissions. As classified by DRG code, alimentary tract disorder may mean a trivial condition such as nausea or a more serious complication like gastrointestinal bleeding. Likewise, electrolyte disorder can range from minor hyperkalemia requiring intravenous hydration to diabetic ketoacidosis causing coma. The severity of illness may not be evident at the time of initial evaluation. In clinical practice, recipients presenting with these symptoms may benefit from an intermediate level of observation before the decision is made to readmit. Intermediate monitoring may help tease out which recipients will improve with minimal intervention and which require further hospitalization.

Following SPK, each decade increase in recipient age, to a threshold of 40 years, was associated with an 11% lower risk of readmission. This is in contrast to our published findings in KTA. Following KTA, for recipients under age 40, each decade increase in age was associated with a 6% higher risk of readmission. One potential explanation for this discrepancy is that young diabetic patients may be less compliant with post-transplant care, as well as general management of their diabetes. Adherence to medication regimens and maintenance of glycemic control is particularly poor among adolescents and young adults with type 1 diabetes (81-86). Poor post-transplant compliance among young SPK recipients could contribute to a higher need for readmission.

Our study demonstrates that African American donor race is associated with an increased risk of readmission. This finding is consistent with inclusion of African American donor race in the pancreas donor risk index (PDRI). In creation of the PDRI, Axelrod et al. demonstrated that African American donor race is associated with a 27% increased risk of graft failure (87). Our study also demonstrates that *recipient* race is not associated with readmission. This finding is in contrast to the association between African American *recipient* race and inferior graft survival (88, 89).

Each day increase in length of stay was associated with a 2% higher risk of readmission until 14 days, beyond which each day increase was associated with a 1% reduction in the risk of readmission. The mechanism of this association is difficult to ascertain and likely complex. Prolonged length of stay can be due to medical complications, for example, delayed graft function, surgical site infection, or graft pancreatitis. Prolonged length of stay can also be secondary to non-medical factors, for example, poor understanding of new medication regimens, increased distance from the hospital, lack of family support at home, or even day of the week. In our study, a short length of stay was likely associated with a low risk of readmission because recipients discharged early tend to be low-risk themselves. These recipients are less likely to require readmission. On the other end of the spectrum, recipients with extremely prolonged hospitalization may not require readmission because their care has been optimized prior to discharge.

Certain factors associated with post-KTA EHR were not associated with post-SPK EHR. Donor type (deceased, living, ECD, DCD) is associated with EHR following KTA. All SPK transplants are performed using deceased donor organs and only a very small percentage of donors are classified as ECD or DCD (0.3% and 2.3%, respectively), making this factor less likely to

contribute to organ quality and subsequent readmission. At the center-level, there was no correlation between readmission for SPK and readmission for KTA, suggesting that mechanistically these two types of readmissions are unique and independent of center-level practices.

Our study has several notable limitations. To ascertain EHR we had to limit our study population to SPK recipients with Medicare as their primary insurance. Inclusion of only Medicare primary patients could differentially affect younger and older recipients and limit generalizability. However, since all individuals with end stage renal disease requiring dialysis are eligible for Medicare, we believe this will minimally affect our results. In fact, the median and interquartile range for age of SPK recipients in our study and among all SPK recipients captured by SRTR was identical (median 40, IQR 34-46). Factors explored in our analysis were limited to those currently collected through the Scientific Registry of Transplant Recipients. As such, we were unable to ascertain certain factors that may be important to post-SPK outcomes, for example mode of dialysis, blood transfusions, and post-surgical complications. Furthermore, in using national registry data we are unable to ascertain more granular factors, like socioeconomic status, which may confound some of our findings. Due to the relatively low national volume of SPK compared to KTA, we may be underpowered to detect an association between center-level factors and EHR.

In conclusion, readmission of SPK recipients occurs with high frequency and though there is variation in the rate of EHR by transplant center, almost all of that variation is explained by differences in patient characteristics rather than differences in center-level practice. Younger SPK recipients are at higher risk for readmission and may benefit from better transitions of care and more frequent outpatient monitoring. The most common reasons for readmission were infection, kidney/urinary tract disorder, and pancreatic/hepatobiliary disorder. Readmission to treat infection or allograft complications may ultimately prevent the development of more serious post-

transplant complications. Given the technical complexity of SPK and the high risk of diabetic complications among recipients, readmission may reflect clinical necessity rather than poor quality of care.

Table 4.1: Study population characteristics, by early hospital readmission (EHR). Table on next page.

	No EHR, n= 1,622	EHR, n=2,021	p-value
Mean Age, SD (years)	40.4, 8.0	39.9, 8.4	0.03
Female, %	34.7	36.6	0.2
African American race, %	18.4	22.4	0.004
Recipient BMI (kg/m2), %			0.5
Underweight (<18.5)	2.5	3.1	
Normal (18.5-25)	54.3	55.5	
Overweight (25-30)	31.8	30.1	
Obese (>30)	11.3	11.3	
Hypertension, %	80.5	79.7	0.5
Cancer, %	0.3	0.4	0.7
Hepatitis C Positive, %	3.9	3.6	0.6
Chronic Obstructive Pulmonary Disease, %	0.9	1.2	0.3
Type 1 Diabetes, %	49.7	48.7	0.5
Current Smoker, %	5.9	6.6	0.4
Congestive Heart Failure	12.4	12.5	0.8
Cerebrovascular Disease	2.7	3.6	0.1
Peripheral Vascular Disease	9.5	10.7	0.2
Mean Dialysis Vintage, SD (years)	2.6, 1.9	2.6, 2.0	0.9
Mean Donor Age, SD (years)	25.7, 9.9	26.0, 10.1	0.5
Female Donor, %	31.3	30.8	0.7
Donor Race, %			0.001
Caucasian	67.6	64.0	
African American	13.6	18.1	
Other	18.7	17.9	
Donor BMI (kg/m2), %			0.003
Underweight (<18.5)	9.9	7.3	
Normal (18.5-25)	48.0	45.0	
Overweight (25-30)	31.8	38.0	
Obese (>30)	10.2	9.6	
Donor Type, %			0.8
Standard Criteria	97.4	97.4	
Extended Criteria	0.3	0.4	
Donation after cardiac death	2.4	2.2	
Donor Cause of Death, %			0.4
Anoxia	12.2	10.6	
Cerebrovascular Accident	17.8	19.0	
Head Trauma	67.1	67.7	
Other	2.9	2.7	
Terminal creatinine >2.5 mg/dL, %	0.56	1.24	0.03
Mean Length of Stay, SD (days)	14.1, 18.2	12.8, 9.9	0.02
Zero HLA Mismatch	2.3	1.8	0.3
Mean Cold Ischemia Time, SD (hours)	12.3, 6.2	12.2, 5.8	0.9
Received Induction Therapy, %	78.8	80.6	0.2
Delayed Graft Function, %	10.3	11.7	0.2
Exocrine Drainage			0.06
Enteric	87.2	84.7	
Bladder	9.1	11.5	
Unknown	3.7	3.8	

Table 4.2: Reason for early hospital readmission after simultaneous pancreas kidney transplantation, n=2,021.

	SPK Recipients Experiencing EHR, n (%)	Required Medical Management, n (%)	Required Surgical/Procedural Management, n (%)
Infection	466 (23.1)	389 (83.5)	77 (16.5)
Kidney/Urinary Tract Disorder	328 (16.2)	294 (89.7)	34 (10.4)
Alimentary Tract Disorder	316 (15.6)	289 (91.5)	27 (8.5)
Pancreatic/Hepatobiliary Disorder	226(11.1)	150 (66.4)	76 (33.6)
Electrolyte/Nutritional Disorder	209 (10.3)	209 (100)	0 (0)
Hematologic /Immunologic Disorder	91(4.5)	89 (97.8)	2 (2.2)
Neurologic Disorder	86 (4.3)	86 (100)	0 (0)
Unspecified Operative Procedure	59 (2.9)	0 (0)	59 (100)
Rehabilitation	47 (2.3)	47 (100)	0 (0)
Unknown Diagnosis	47 (2.3)	-	-
Cardiac	41 (2.0)	37 (90.2)	4 (9.3)
Other			
Diagnosis unrelated to SPK	34 (1.7)	12 (35.3)	22 (64.7)
Vascular Disorder	24 (1.2)	13 (54.2)	11 (45.8)
Respiratory Disorder	14 (0.7)	8 (57.1)	6 (42.9)
Wound/Skin Breakdown	12 (0.7)	5 (41.7)	10 (83.3)
Diabetes/Endocrine Disorder	8 (0.4)	7 (87.5)	1 (12.5)
Scheduled Follow-up	5 (0.3)	5 (100)	0 (0)
Musculoskeletal/Connective Tissue Disorder	4 (0.2)	4 (100)	0 (0)
Drug Complications	3 (0.2)	3 (100)	0 (0)
Psychiatric Disorder	1 (0.1)	1 (100)	0 (0)

Table 4.3: Relative risk of early hospital readmission after simultaneous pancreas-kidney transplantation, n=3,643.

Factors	Adjusted Relative Risk (95% CI)	p-value
Age (per decade)		
18 to 40 years	0.88 (0.82, 0.97)	0.005
Greater than 40 years	1.05 (0.97, 1.15)	0.2
Recipient African American Race	1.07 (0.98, 1.16)	0.1
Recipient BMI (kg/m2)		
Underweight (<18.5)	1.09 (0.94, 1,28)	0.3
Normal (18.5-25)	REF	-
Overweight (25-30)	0.96 (0.87, 1.06)	0.4
Obese (>30)	0.90 (0.68, 1.19)	0.5
Peripheral Vascular Disease	1.10 (0.99, 1.23)	0.07
Donor African American Race	1.13 (1.04, 1.23)	0.005
Donor Asian Race	1.06 (0.97, 1.16)	0.2
Donor BMI (kg/m2), %		
Underweight (<18.5)	0.91 (0.78, 1.06)	0.2
Normal (18.5-25)	REF	-
Overweight (25-30)	1.12 (1.04, 1.22)	0.004
Obese (>30)	1.04 (0.92, 1.19)	0.5
Lack of Induction	1.06 (0.98, 1.16)	0.2
Length of stay (per day)		
First 14 days	1.02 (1.01, 1.04)	<0.001
Greater than 14 days	0.99 (0.98, 0.99)	<0.001

Table 4.4: Relative risk of early hospital readmission after simultaneous pancreas-kidney transplantation by center-level factors, n=3,643.

Factors	Adjusted Relative Risk (95% CI)	p-value
Total volume		
1-11	REF	-
12-27	1.18 (0.85, 1.63)	0.3
29-122	0.98 (0.73, 1.33)	0.7
Average length of stay (days)		
4.8- 11.1	REF	-
11.1- 14.6	0.99 (0.79, 1.23)	0.9
14.7- 47.7	1.04 (0.82,1.33)	0.7
Percent African American recipients		
0- 7.7%	REF	-
8.1- 21.4%	1.06 (0.84,1.34)	0.5
22.2- 100%	1.06 (0.82, 1.36)	0.5
Median time to transplant (years)		
0.1- 0.7	REF	-
0.7- 1.3	1.21 (0.97, 1.49)	0.09
1.3- 3.7	1.11 (0.89, 1.39)	0.3
Percent Preemptive Transplant		
0- 4.5%	REF	-
4.6- 13.3%	0.94 (0.75, 1.19)	0.6
13.8- 66.7%	1.12 (0.88, 1.43)	0.3

Figure 4.1: Ratio of observed to expected probability of early hospital readmission after simultaneous pancreas-kidney transplantation for each transplant center. The observed probability of EHR was calculated for each center. Based on each center's case mix an expected probability of EHR was derived from the final model. Each dot represents the ratio of observed to expected probability of EHR for a given transplant center. A center that readmits exactly as many patients as expected falls on the reference line. Those that admit less than expected fall below the reference line and those that admit more than expected fall above the reference line.

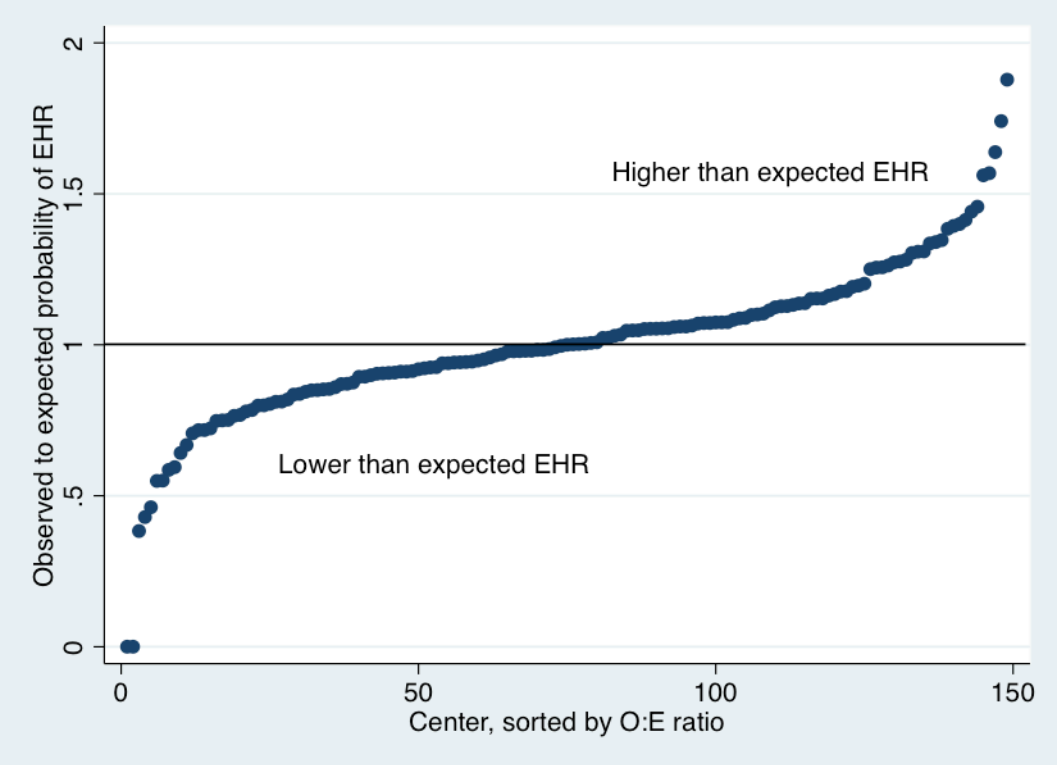
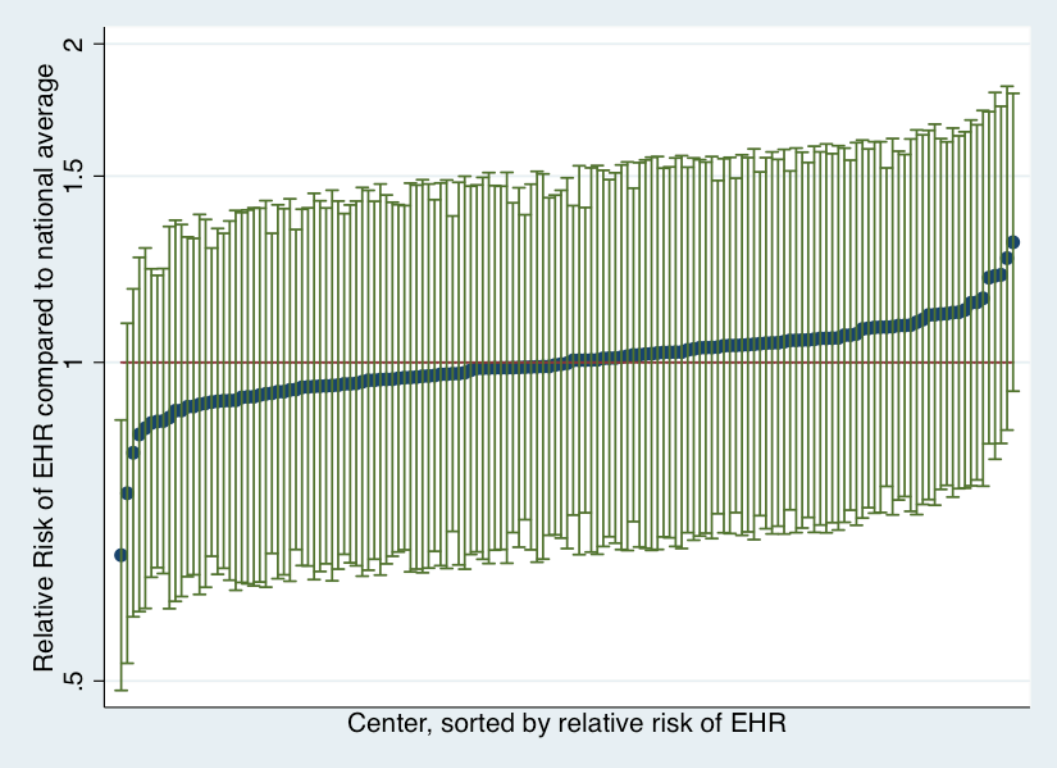


Figure 4.2: Relative risk of early hospital readmission after simultaneous pancreas-kidney transplantation by transplant center compared to national average. Each dot represents the relative risk of EHR for each transplant center in the United States, with 95% confidence interval. The confidence interval for all but one of the transplant centers overlaps the reference line, which represents the national average for EHR following SPK.



CHAPTER 5: IMPACT OF READMISSION FOLLOWING PANCREAS KIDNEY TRANSPLANTATION

SUMMARY:

We recently showed that 54% of simultaneous pancreas-kidney recipients experience early hospital readmission. To guide clinical management of these recipients, it is vital to understand whether early hospital readmission is associated with post-transplant outcomes, specifically late hospital readmission, death-censored graft loss, and mortality. We used United States Renal Data System data to study 3,054 adult Medicare primary first-time simultaneous pancreas-kidney recipients from December 1999-October 2011. Early hospital readmission was any hospitalization within 30 days of transplant discharge. Late hospital readmission was any hospitalization occurring between 30 days and 1 year after transplant discharge. Recipients experiencing early hospital readmission were at a higher risk of experiencing late hospital readmission (aRR $_{1.35}1.57_{1.98}$, $p<0.001$). During readmission, recipients were at a higher risk of pancreas graft loss (aHR $_{7.80}14.2_{25.8}$, $p<0.001$), a higher risk of kidney graft loss (aHR $_{5.34}18.4_{63.2}$, $p<0.001$) and a higher risk of mortality (aHR $_{2.08}8.5_{34.8}$, $p=0.003$). Immediately following readmission, the risk of graft loss and mortality dropped substantially, but remained elevated for pancreas graft loss (aHR $_{1.17}1.45_{1.80}$, $p=0.001$) and kidney graft loss (aHR $_{1.17}1.46_{1.81}$, $p=0.001$). Post-readmission there was no difference in the hazard of mortality comparing recipients that previously experienced readmission to recipients without readmission ($_{0.99}1.25_{1.57}$, $p=0.055$). Readmission following simultaneous pancreas-kidney transplantation substantially increases the risk of graft loss and mortality during the readmission hospitalization and post-readmission.

INTRODUCTION

Based on national registry data, we recently demonstrated that 54% of simultaneous pancreas-kidney transplantation (SPK) recipients are readmitted within 30 days of discharge following initial SPK hospitalization. Clinical characteristics associated with early hospital readmission (EHR) were limited to younger recipient age, African American donor, and increased length of stay (12). Our ability to predict which SPK recipients will experience EHR remains limited, however understanding the clinical implications of readmission can guide management of these individuals during the EHR hospitalization and post-EHR.

In other populations, readmission is associated with clinical outcomes (41, 42, 44, 46-49, 51, 90-92). Among community dwelling older adults, EHR is associated with a 3-fold increase in one-year mortality (44). Similarly, adults with advanced liver disease who are readmitted within 30 days of hospitalization have a 2.6-fold increase in 90-mortality (90). Readmission is also associated with increased mortality following cancer resection, abdominal aortic aneurysm repair, and percutaneous coronary interventions (41, 42, 46-48, 91, 92). In the field of transplantation, EHR is a strong predictor of outcomes following kidney transplantation alone (KTA). Previous work from our group, using national registry data, found that EHR is associated with increased hospitalization within the first year following KTA. In addition, EHR following deceased donor KTA is associated with a 1.43-fold increase in the risk of graft loss and a 1.50-fold increase in the risk of mortality (2).

The objective of this study was to quantify the association between EHR following SPK and survival during two distinct time periods: the EHR hospitalization and post-EHR. A second objective of this study was to quantify the association between EHR and subsequent hospitalization within the first year following SPK.

METHODS

Study Population

The study population included 3,054 adult first-time SPK recipients from December 1, 1999 through October 31, 2011 who had Medicare Part A and B as their primary insurance for at least 60 days before and 60 days following the date of transplant. Donor, recipient, and transplant characteristics were obtained from Organ Procurement Transplantation Network data. This study was reviewed by the institutional review board at Johns Hopkins School of Medicine and determined to qualify for an exemption under 45 CFR 46.101(b) as study participants cannot be identified directly or through linked identifiers.

Exposure and Outcome Ascertainment

EHR was captured using United States Renal Data System (USRDS) claims data. As specified in our previously published models of EHR following SPK, EHR was defined as any hospitalization to an acute care facility within 30 days of discharge after initial SPK hospitalization (12). Late hospital readmission (LHR) was any hospitalization occurring between 30 days and 1 year after initial transplant discharge. SPK recipients that died prior to discharge were excluded (n=136). SPK recipients that had either pancreas or kidney graft loss prior to discharge, but did not die, were also excluded from the analysis (n=203) because readmission in a recipient with a functioning graft at the time of discharge is mechanistically different than readmission of a recipient that has already lost their graft.

Association between EHR and LHR

The association between EHR and LHR was estimated using modified Poisson regression, as previously described (13). The model was adjusted for recipient, donor, and transplant characteristics (recipient age, African American donor, and length of stay) known to be associated with EHR, based on our previously published national model (12).

Association Between EHR and Survival

Cox proportional hazard models were used to estimate the hazard of death-censored graft loss and mortality associated with EHR. Separate models were used to estimate pancreas graft loss and kidney graft loss. Since the Scientific Registry of Transplant Recipients (SRTR) does not currently have a risk adjustment model for pancreas graft loss, our model for pancreas graft loss was adjusted for recipient, donor, and transplant characteristics (recipient age, recipient BMI, total end stage renal disease time, donor age, donor sex, African American donor, Asian donor, donor BMI, donor height, donor cause of death, DCD, terminal creatinine >2.5mg/dL, and cold ischemia time) based on the SRTR risk adjustment model for SPK recipient survival (50). Our model for recipient mortality was adjusted for these same characteristics. Our model for kidney graft loss was adjusted for recipient, donor, transplant characteristics (donor age, HLA mismatch, time on dialysis) based on the SRTR risk adjustment model for kidney graft loss following SPK (50). Recipients were censored at 5 years of follow-up, time of re-transplant, or administratively. We used a clustered sandwich estimator for standard errors to account for possible center-level correlation. The proportional hazard assumption for each model was confirmed visually using log-log plots and Schoenfeld residuals.

The hazard of death-censored graft loss and mortality was estimated for two distinct time periods: from EHR admission date to EHR discharge or death/graft loss (EHR hospitalization) and from EHR discharge date to death/graft loss or censorship (post-EHR). To avoid immortal person-time bias among SPK recipients with EHR (requiring patient and graft survival up to the point of readmission) we used a standard method of late entries in which the recipients with EHR only contributed to the exposed risk set starting at the time of admission for the EHR hospitalization. Based on exploratory data analysis and prior hypotheses, the attributable hazard during the EHR hospitalization and post-EHR were treated as constant. In other words, the estimate for "EHR hospitalization" represents the hazard averaged over the entire hospitalization while the "post-

EHR" hazard represents the hazard averaged over the amount of time since EHR discharge.

Statistical Analysis

Confidence intervals are reported as per the method of Louis and Zeger, as previously described (14, 15). All analyses were performed using STATA 14.0/MP for Linux (Stata Corp LP, College Station, TX, USA).

RESULTS

Early Hospital Readmission

Of 3,053 SPK recipients, 1,701 experience EHR (55.7%) (Table 5.1). The median time from transplant discharge to EHR admission was 7 days (IQR 3-13. Among recipients who experienced EHR, the length of stay for the EHR hospitalization ranged from 0 to 152 days with a median length of stay of 4 days (IQR 2-8).

Late Hospital Readmission

Among all recipients, 9.8% experienced at least one LHR. Only 1.1% of recipients experienced greater than one LHR. In a multivariate model adjusted for recipient, donor, and transplant characteristics, EHR was associated with a 1.57-fold increase in the risk of LHR ($aRR_{1.25}1.57_{1.98}$, $p<0.001$).

Crude Death-censored Graft Loss and Mortality

Crude death-censored pancreas graft loss within 30 days of transplant discharge was 1.6% for recipients who experienced EHR and 0.5% for recipients without EHR (p=0.001). Crude death-censored kidney graft loss within 30 days of transplant discharge was 0.3% for recipients who experienced EHR and 0.2% for recipients without EHR (p<0.6). Crude mortality within 30 days of transplant discharge was 0.4% for recipients who experienced EHR and 0.4% for recipients

without EHR (p=0.8). Crude one-year death-censored pancreas graft loss was 5.1% for recipients who experienced EHR and 2.6% for recipients without EHR (p<0.001). Crude one-year death-censored kidney graft loss was 3.2% for recipients who experienced EHR and 1.6% for recipients without EHR (p<0.002). Crude one-year mortality was 2.9% for recipients who experienced EHR and 1.9% for recipients without EHR (p=0.09).

Association Between EHR and Survival During the EHR Hospitalization Time Period

During the EHR hospitalization, 1.8% (n=30) of recipients lost their pancreas graft. The median time to death-censored pancreas graft loss was 2 days (IQR 1-7), with 6 recipients losing their graft on the same day as EHR admission. During the EHR hospitalization, 0.6% (n=10) of recipients lost their kidney graft. The median time to death-censored kidney graft loss was 19 days (IQR 6-44 days). No recipients lost their kidney graft on the same day as EHR admission. During the EHR hospitalization, 0.5% (n=8) of recipients died. The median time to death was 30 days (IQR 17-68 days), with no recipients dying on the same day as EHR admission. In an adjusted model, during the EHR hospitalization, recipients who experienced EHR were 14.2-times more likely to lose their pancreas graft (aHR $_{7.80}14.2_{25.8}$,p<0.001) and 18.4-times more likely to lose their kidney graft compared to recipients without EHR (aHR $_{5.34}18.4_{63.2}$, p<0.001) (Table 5.2). During the EHR hospitalization, recipients who experienced EHR were 8.5-times more likely to die compared to recipients without EHR (aHR $_{2.08}8.5_{34.8}$,p<0.003).

Association Between EHR and Survival During the Post-EHR Time Period

During the post-EHR time period 12.0% (n=196) of recipients who previously experienced EHR lost their pancreas graft. The median time to death-censored pancreas graft loss was 724 days (IQR 234-1185 days), with 26 recipients losing their pancreas graft within 30 days of post-EHR discharge. During the post-EHR time period 14.4% (n=214) recipients who previously experienced EHR lost their kidney graft. The median time to death-censored kidney graft loss of

791 days (IQR 462-1243), with 5 recipients losing their kidney graft within 30 days of post-EHR discharge. During the post-EHR time period, 8.9% (n=151) of recipients who previously experienced EHR died. The median time to death of 883 days (IQR 314-1270), with 7 recipients dying within 30 days of post-EHR discharge In an adjusted model, during the post-EHR time period, recipients who previously experienced EHR were 1.45-times more likely to lose their pancreas graft (aHR $_{1.17}1.45_{1.80}$, p=0.001) and 1.46-times more likely to lose their kidney graft compared to recipients without EHR (aHR $_{1.17}1.46_{1.81}$, p=0.001) (Table 5.2). During the post-EHR time period, there was no difference in the hazard of mortality comparing recipients who previously experienced EHR to recipients without EHR (aHR $_{0.99}1.25_{1.57}$, p=0.055).

DISCUSSION

In this national study of 3,54 SPK recipients, we found that that EHR is associated with LHR, pancreas graft loss, kidney graft loss, and mortality. We also found that the association between EHR and adverse transplant outcomes is dynamic. During the readmission hospitalization, pancreas graft loss was 14.2-times higher and kidney graft loss was 18.4-times higher. Similarly, mortality was 8.5-times higher. Immediately following readmission discharge, the hazard of graft loss remained elevated, but much less so. Pancreas graft loss was 1.45-times higher and kidney graft loss was 1.46-times higher. Post-EHR there was no difference in the hazard of mortality for recipients who previously experienced EHR compared to recipients without EHR.

Our study is the first to quantify the association between EHR following SPK and adverse clinical outcomes. We found that EHR is associated with a higher risk of LHR, graft loss, and mortality, which is consistent with our previous work on EHR following KTA. In our previous work on EHR following KT, we found that EHR was associated with a 3.02-fold increase in the risk of LHR, a 1.43-fold increase in the risk of graft loss, and a 1.50-fold increase in the risk of mortality (2). Following a variety of other surgical procedures, such as pancreatectomy, coronary artery

bypass grafting, orthopedic surgery, colectomy, and cancer resection, the hazard of mortality associated with EHR ranges from 2.3 to 6.6 (41, 42, 46-49, 51). However, prior work on the association between EHR and mortality may be misleading. These studies average the risk attributable to EHR over the entire follow-up period. The risk of mortality for patients who are acutely ill and readmitted to the hospital is assumed to be the same as the risk of mortality for a patient that previously experienced EHR, survived, and may be months or years post-EHR. Our study of EHR following SPK provides an understanding of the timeline of risk, showing that that the risk is highest during the EHR hospitalization and decreases substantially post-EHR.

Our findings may have practical implications for management of SPK recipients experiencing EHR. The readmission hospitalization represents a high-risk event in the post-SPK timeline. Overall, recipients experiencing EHR should be managed cautiously. Our findings suggest that pancreas graft loss is more likely to occur during the first week of EHR hospitalization. Early and frequent surveillance of pancreas graft function following transplant discharge may help mitigate this risk. In addition, we found that kidney graft loss and mortality occurred much later into the EHR hospitalization. In recipients with prolonged EHR hospitalization, more aggressive management may help rescue these individuals. Following readmission discharge, the risk of graft loss was attenuated, but did not disappear completely. More importantly, a small proportion of recipients that were previously readmitted lost their graft or died within 30 days of the readmission discharge. Comprehensive discharge planning, frequent outpatient follow-up, and regular communication between the recipient and transplant providers may help decrease the risk immediately post-EHR.

Our study had several notable limitations. EHR was ascertained using Medicare claims data and therefore our study population is limited to Medicare-primary KT recipients. Medicare is the leading primary insurer for nearly half of all KT recipients. Our study captures an important, and

large, portion of KT recipients nationally. Furthermore, all individuals with end stage renal disease are eligible for Medicare, regardless of age or disability. Another limitation of using national registry data is that we are unable to determine whether recipients lost their graft during the readmission or if they were readmitted because they were already losing their graft. This is a concern for pancreas graft loss since 6 recipients lost their graft on the day of readmission and 75% lost their graft within the first 7 days. It is less of a concern for mortality and kidney graft loss, which on average occurred much later into the EHR hospitalization. Although we cannot prove a causal pathway between EHR and adverse outcomes, our study is the first to explore the attributable risk associated with EHR following SPK.

Early hospital readmission is common following SPK and it portends a substantial risk of graft loss and mortality. Recipients experiencing EHR should be managed with caution, as they are more susceptible to adverse outcomes both during the EHR hospitalization and post-EHR.

Table 5.1: Study population characteristics, by early hospital readmission, n=3,054.

	No Early Hospital Readmissions n=1,353	Early Hospital Readmissions n= 1,701	p-value
Median Age, IQR (years)	40, 34-46	39, 33-46	0.04
Female, %	34.8	35.7	0.6
African American race, %	18.3	22.0	0.004
Recipient BMI (kg/m2), %			0.2
Underweight (<18.5)	2.2	3.4	
Normal (18.5-25)	55.6	56.3	
Overweight (25-30)	31.8	29.7	
Obese (>30)	10.4	10.7	
Mean dialysis vintage, IQR (years)	2.2, 1.2-3.5	2.2, 1.2-3.5	0.6
Mean ESRD time, IQR (years)	2.5, 1.4-3.8	2.4, 1.4-3.7	0.3
Median donor age, IQR (years)	23, 18-31	23, 18-33	0.2
Female donor, %	30.7	30.9	0.8
African American donor	13.8	18.9	<0.001
Asian donor	1.7	2.5	0.1
Donor BMI (kg/m2), %			0.01
Underweight (<18.5)	7.4	5.3	
Normal (18.5-25)	59.4	56.8	
Overweight (25-30)	26.6	31.0	
Obese (>30)	6.7	7.1	
Median donor height, IQR (meters)	1.7, 1.7-1.8	1.7 , 1.7-1.8	0.8
Donation after cardiac death	1.9	2.1	0.7
Donor Cause of Death, %			0.3
Anoxia	11.9	10.8	
Cerebrovascular Accident	17.4	18.6	
Head Trauma	67.4	68.1	
Other	3.3	2.5	
Terminal creatinine >2.5 mg/dL, %	0.7	1.2	0.1
Median length of stay, IQR (days)	9, 7-13	9, 8-14	0.03
HLA match, %			0.5
0	1.9	1.3	
1	1.0	0.6	
2	2.7	3.4	
3	12.7	11.8	
4	25.5	26.7	
5	33.5	35.1	
6	22.8	21.6	
Median Cold Ischemia Time, IQR (hours)	11.4, 8.0-15.5	11.3, 8.2-15	0.8

Table 5.2: Hazard of death-censored graft loss and mortality during readmission hospitalization (readmission hospitalization) and following readmission discharge (post-readmission).

	Readmission Hospitalization	Post-Readmission
Pancreas graft loss	$_{7.80}14.2_{25.8}$	$_{1.17}1.45_{1.80}$
Kidney graft loss	$_{5.34}18.4_{63.2}$	$_{1.17}1.46_{1.81}$
Mortality	$_{2.08}8.5_{34.8}^{*}$	$_{0.99}1.25_{1.57}^{**}$

*p=0.003, **p=0.055, all other p-values < 0.001

DISCUSSION AND FUTURE PLANS

Through this thesis work, we have examined clinical mechanisms, novel predictors, and the time-varying impact of EHR following kidney transplantation and simultaneous pancreas-kidney transplantation. We built a framework for the development of clinical practices aimed at preventing readmission. WE have also provided valuable knowledge for clinical decision making for recipients experiencing EHR.

First, we used granular single-center data to characterize the clinical scenarios in which EHR occurs at our own transplant center. We showed that the majority of readmissions occur directly to the hospital without prior evaluation by a healthcare provider. We showed that infection was the most common reason for readmission, with the urinary tract as the most likely source. We also found that a subset of readmissions were more complex and not due to one primary reason. At our center, which performs many transplants with desensitization and has an infrastructure established for these complex recipients, we found no difference in the rate of readmission comparing desensitized recipients to other recipients. We observed no association between EHR and HRQOL, cognitive function, functional status, or physical function. A potential explanation is that kidney transplant recipients are selected based on many of these variables and our KT population overall had high HRQOL and high cognitive and physical function. We also found no association between EHR and socioeconomic factors. A potential explanation is that the decision to readmit is based on clinical characteristics rather than socioeconomic factors. A second explanation may be that all KT recipients, regardless of socioeconomic factors, are closely monitored following initial KT discharge.

We next used national registry data to explore the association between EHR and social determinants of health. Again, we found no association between EHR and socioeconomic status. We explored the independent association between EHR and community risk and found that the health behaviors of individuals living near KT recipients are associated with EHR. Recipients living in low-intermediate, high-intermediate, and highest risk communities were at increased risk of readmission. In addition, EHR was inversely associated with distance from transplant center. Recipient living within 10 miles of their transplant center were at highest risk of readmission. These findings support our hypothesis that factors above and beyond clinical characteristics contribute to EHR and should be considered in strategies to predict and reduce EHR.

Next, we explored the time-varying impact of EHR. We determined the hazard of graft loss and mortality associated with EHR during two distinct time periods: the EHR hospitalization and post-EHR. We hypothesized that the risk would be higher during the EHR hospitalization and would decrease post-EHR. We showed that compared to recipients without EHR, recipients experiencing EHR were at a substantially higher risk of both graft loss and mortality during the EHR hospitalization. Immediately following EHR discharge, the risk dropped substantially. However, compared to recipients without EHR, recipients that previously experienced EHR remained at an elevated risk of both graft loss and mortality for approximately 5 years following readmission.

We also used national registry data to explore EHR following SPK. We found that 54% of SPK recipients experience EHR, a much larger proportion compared to KT alone, likely owing to the increased surgical complexity of SPK. Few patient-level characteristics were associated with EHR, making it difficult to predict which SPK recipients are at highest risk. Younger SPK recipients were at an increased risk of EHR, making this population a potential sub-group to target. Younger recipients may benefit from detailed discharge planning and more frequent

outpatient follow-up. The most common reasons for readmission were infection, kidney/urinary tract disorder, and pancreatic/hepatobiliary disorder. Prompt management of these conditions may prevent more serious complications in the long-term.

Finally, we found that EHR substantially increases the risk of both pancreas and kidney graft loss during the EHR hospitalization, and that risk drops substantially following readmission discharge. We also found that EHR is associated with an increased risk of mortality during the EHR hospitalization. However, compared to recipients without EHR, there was no difference in the risk of mortality post-EHR. These findings suggest that recipients experiencing EHR following SPK should be managed with caution as they are more susceptible to adverse outcomes both during the EHR hospitalization and post-EHR. Aggressive management during the EHR hospitalization, as well as detailed discharge planning, frequent follow-up, and open communication between the recipient and the transplant team may help decrease the risk of adverse outcomes during the EHR hospitalization and post-EHR.

Our findings build the foundation for future work, which will focus on preventing unnecessary readmission and improving patient outcomes for recipients that experience EHR. Within our own center, prevention and early rescue of infection may be an area for potential impact. During the initial transplant hospitalization, prior to discharge, and throughout early outpatient follow-up, our transplant providers can have a high index of suspicion and a low threshold to treat infection. An important finding at our center was that the majority of readmissions occurred directly from home. We plan to implement an outpatient area, separate from our regularly scheduled clinics, where a transplant provider can evaluate transplant patients with acute issues. This would facilitate early diagnostic testing and may even enable a cost-effective forum for treatment of low acuity conditions. An intermediate level of evaluation, prior to readmission, would allow our transplant providers to collect information and make an informed decision about the need for

hospitalization. In addition, earlier evaluation by a transplant provider would eliminate any delay in management for recipients presenting with critical issues.

In addition to developing interventions to address EHR at our own center, we plan to further explore the impact of social determinants of health on readmission following SPK. Ultimately, our goal is to build a comprehensive, easy to use, risk prediction tool for EHR. Using our existing national models, which incorporate both clinical and social characteristics, we will classify recipients as low, intermediate, or high risk of EHR. We will then prospectively test the discriminative ability of our prediction tool in a cohort of kidney transplant recipients at our own transplant center. If effective, recipients at high risk of experiencing EHR could be assigned more frequent outpatient clinic visits, regular phone calls from a provider, and a specific list of clinical symptoms that should prompt a call to the transplant team.

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The following manuscripts, which were designed and conducted by Dr. King and for which Dr. King was the first author or co-first author (*), comprise this thesis:

Chapter 1: Craig-Schapiro R*, King EA*, Lin JA, McAdams-DeMarco MA, Al-Ammary F, Desai NM, Segev DL. Mechanisms of Early Hospital Readmission Following Kidney Transplantation. In preparation.

Chapter 2: King EA, Kucirka LM, O'Hare MA, McAdams-DeMarco MA, Massie AB, Al-Ammary F, Desai NM, Schold JD, Segev DL. The Impact of Community Risk and Other Social Determinants of Health on Early Hospital Readmission following Kidney Transplantation. In preparation.

Chapter 3: King EA, Bowring MG, Massie AB, Kucirka LM, McAdams-DeMarco MA, Al-Ammary F, Desai NMN, Segev DL. Mortality and Graft Loss Attributable to Readmission following Kidney Transplantation: Immediate and Long-Term Risk. In preparation.

Chapter 4: King EA, Kucirka LM, McAdams-DeMarco MA, Massie AB, Al-Ammary F, Ahmed R, Grams ME, Segev DL. Early Hospital Readmission After Simultaneous Pancreas-Kidney Transplantation: Patient and Center-Level Factors. Am J Transplant. 201616(2):541-9.

Chapter 5: King EA, Kucirka LM, McAdams-DeMarco MA, Massie AB, Bowring MG, Al-Ammary F, Desai NM, Segev DL. Impact of Early Hospital Readmission Following Simultaneous Pancreas Kidney Transplantation. In preparation.

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PERMISSIONS FOR BIBLIOGRAPHY

AMERICAN JOURNAL OF TRANSPLANTATION

CURRICULUM VITAE

Elizabeth A. King, M.D.
Categorical Resident and Research Fellow, General Surgery
Johns Hopkins University School of Medicine

Department of Surgery
Division of Transplant Surgery
Johns Hopkins Hospital
720 Rutland Ave, Turner 34
Baltimore, MD 21205
Tel: 630-244-6464
Email: eking19@jhmi.edu

EDUCATION, TRAINING, AND PROFESSIONAL EXPERIENCE

Years	Degree	Institution	Discipline
2002-2006	B.S.	University of Illinois	Biochemistry
2006-2010	M.D.	University of Chicago	Medicine
2010-2011	Internship	Johns Hopkins Hospital	General Surgery
2011-2012	Junior Residency	Johns Hopkins Hospital	General Surgery
2012-present	Senior Residency	Johns Hopkins Hospital	General Surgery
2013-present	Research Fellowship	Johns Hopkins Hospital	Transplant Surgery

RESEARCH ACTIVITIES

Peer-reviewed Original Research Articles:

1. Ison MG, Llata E, Conover CS, Friedewald JJ, Gerber SI, Grigoryan A, Heneine W, Millis JM, Simon DM, Teo CG, Kuehnert MJ; Contributors: Ramachandran S, Seem D, Drobeniuc J, Durant T, Easton J, Ganova-Raeva L, Garcia-Lerma G, Holmberg S, Khudyakov Y, Kumar L, Lin Y, Millis M, Minske B, Owen S, Ponterelli J, Sullivan K, Switzer WM, Youngpairoj AS, Xia GL, Mozes M, Smith A, DeMayo E, Stosor V, Forrest Dodson S, **King EA**. Transmission of human immunodeficiency virus and hepatitis C virus from an organ donor to four transplant recipients. Am J Transplant. 2011;11(6):1218-25.

2. McAdams-Demarco MA, Grams ME, **King E**, Desai NM, Segev DL. Sequelae of early hospital readmission after kidney transplantation. Am J Transplant. 2014;14(2):397-403.

3. Salter ML, Gupta N, **King E**, Bandeen-Roche K, Law AH, McAdams-DeMarco MA, et al. Health-related and psychosocial concerns about transplantation among patients initiating dialysis. Clin J Am Soc Nephrol. 2014;9(11):1940-8.

4. McAdams-DeMarco MA, Law A, **King E**, Orandi B, Salter M, Gupta N, et al. Frailty and mortality in kidney transplant recipients. Am J Transplant. 2015;15(1):149-54.

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10. Lentine KL, Lam NN, Axelrod D, Schnitzler MA, Garg AX, Xiao H, Dzebisashvili N, Schold JD, Brennan DC, Randall H, **King EA**, Segev DL. Perioperative Complications after Living Kidney Donation: A National Study. Am J Transplant. 2015.

11. Nagarajan N, Morden A, Bischof D, **King E**, Kosztowski M, Wick EC, et al. The role of fiber supplemnetation in the treatment of irritable bowel syndrome: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2015;27(9)1002-1010.

12. Massie AB, Leanza J, Fahmy LM, Chow EK, Desai NM, Luo X, **King EA**, Bowring MG, Segev DL. A Risk Index for Living Donor Kidney Transplantation. Am J Transplant. 2016.

Oral Presentations at National or International Meetings

1. **King EA**, Garonzik-Wang JM, Kumar K, Law AH, Segev DL. Educational Interventions Increase Candidates and Live Donor Champion Comfort with Initiating Conversations about Live Donation. Academic Surgical Congress. San Diego. February 2014.

2. **King EA**, Massie AB, Desai NM, Segev DL. Kidneys from Donation after Cardiac Death Donors are Underutilized in Pediatric Patients. World Transplant Congress. San Francisco. July 2014.

3. **King EA**, Massie AB, Segev DL. Livers from Donation after Cardiac Death Donors are Underutilized in Pediatric Patients. World Transplant Congress. San Francisco. July 2014.

4. **King EA**, McAdams-DeMarco MA, Chow E, Segev DL. Early Hospital Readmission Phenotype: Center-Level Analysis in Kidney Transplantation. World Transplant Congress. San Francisco. July 2014.

5. **King EA**, Wickliffe C, McAdams-DeMarco MA, Segev DL. Comparing Early Hospital Readmission after Kidney Transplantation with Readmission for Non-Transplant Conditions: A Center-Level Analysis. World Transplant Congress. San Francisco. July 2014.

6. **King EA**, McAdams-DeMarco MA, Lentine KL, Axelrod DA, Schnitzler M, Tuttle-Newhall JE, Segev DL. Early Hospital Readmissions after Liver Transplantation: Center Level Rates and Patient Risk Factors. World Transplant Congress. San Francisco. July 2014.

7. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Grams ME, Schold JD, Segev DL. Impact of Community Risk on Early Hospital Readmission following Kidney Transplantation. American Transplant Congress. Philadelphia. May 2015.

8. **King EA**, Bowring MG, Kucirka LM, McAdams-DeMarco MA, Massie AB, , Segev DL. Mortality and Graft Loss Attributable to Readmission following Kidney Transplantation. American Transplant Congress. Boston. scheduled June 2016.

9. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Impact of Early Hospital Readmission following Simultaneous Pancreas-Kidney Transplantation. American Transplant Congress. Massachusetts. scheduled June 2016.

10. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Early Hospital Readmission following Kidney Re-transplantation. American Transplant Congress. Boston. scheduled June 2016.

11. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Early Hospital Readmission following Pediatric Kidney Transplantation. American Transplant Congress. Boston. scheduled June 2016.

12. **King EA**, Garonzik-Wang J, Bowring MG, Kumar K, Segev DL. The Live Donor Champion Program: A Novel Approach to Identifying Live Kidney Donors. American Transplant Congress. Boston. scheduled June 2016.

13. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. The Impact of Readmission following Kidney Transplantation: Is Readmission Becoming More Risky? American Transplant Congress. Boston. scheduled June 2016.

<u>Poster Presentations at National or International Meetings</u>

1. **King EA**, Kahn JP, Erby LH, Segev DL. Assessing Pressure and Coercion to Donate among Candidates for Living Kidney Donation. World Transplant Congress. San Francisco. July 2014.

2. **King EA**, Waldinger S, Segev DL. Early Hospital Readmissions following Kidney Transplantation. A Single Center Descriptive Analysis. World Transplant Congress. San Francisco. July 2014.

3. **King EA,** Kucirka LM, McAdams-DeMarco MA, Massie AB, Schold JD, Segev DL. The Impact of Community Risk on Early Hospital Readmission Following Kidney Transplantation. American Society of Transplant Surgeons 15th Annual State of the Art Winter Symposium. Miami. January 2015.

4. **King EA**, Garonzik-Wang J, Bowring MG, Kumar K, Segev DL. Addressing Low Live Kidney Donation Rates in African Americans through the Live Donor Champion

Program. American Society of Transplant Surgeons 15th Annual State of the Art Winter Symposium. Miami. January 2015.

5. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Early Hospital Readmission Following Kidney Transplantation: Are We Getting Better Over Time? American Society of Transplant Surgeons 15th Annual State of the Art Winter Symposium. Miami. January 2015.

6. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Early Hospital Readmission following Simultaneous Pancreas-Kidney Transplantation. American Transplant Congress. Philadelphia. May 2015.

7. **King EA**, Kucirka LM, McAdams-DeMarco MA, Chow E, Segev DL. Early Hospital Readmission and Distance from Transplant Center. American Transplant Congress. Philadelphia. 2015.

8. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Impact of Early Hospital Readmission following Simultaneous Pancreas-Kidney Transplantation. American Society of Transplant Surgeons 16th Annual State of the Art Winter Symposium. Miami. January 2016.

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11. **King EA**, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Older Recipients and Early Hospital Readmission following Kidney Transplantation. American Society of Transplant Surgeons 16th Annual State of the Art Winter Symposium. Miami. January 2016.

12. **King EA**, Orandi BJ, Luo X, Bae S, Kucirka LM, McAdams-DeMarco MA, Massie AB, Segev DL. Early Hospital Readmission following Incompatible Kidney Transplantation. American Society of Transplant Surgeons 16th Annual State of the Art Winter Symposium. Miami. January 2016.

<u>External Funding, Current</u>

7/1/2013-8/31/2013. American Society for Transplantation/Novartis Clinical Science Fellowship Grant.
Sponsor: American Society for Transplantation
Principal Investigator: King
Role: Principal Investigator
Geriatric-Specific Risks and Outcomes in Older Kidney Transplant Recipients

9/1/2013-8/31/2016. National Institute of Aging, Ruth L. Kirchstein National Research Service Award.
Sponsor: National Institute of Health
Principal Investigator: King
Role: Principal Investigator
Geriatric-Specific Risks and Outcomes in Older Kidney Transplant Recipients

EDUCATIONAL ACTIVITIES

Educational Publications

1. Johns Hopkins ABSITE Review Manual Second Edition (Meguid, Van Arendonk, Lipsett, eds; King, contributing author), Lipencott, Williams & Wilkins. 2013

Teaching Experience

- Teaching Assistant for Clinical Pathophysiology and Therapeutics, 2009-2010 (Pritzker School of Medicine, University of Chicago)
- Clinical Instructor Medical Student Skills Lab, 2013-2016 (Department of Surgery, Johns Hopkins University)
- Clinical Instructor Intern Skills Lab, 2013-2016 (Department of Surgery, Johns Hopkins University)
- Medical Student Orientation to Surgery Clerkship Guest Lecturer, 2015 (Department of Surgery, Johns Hopkins University)
- Epidemiology of Aging Guest Lecturer, 2015 (Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health)

CLINICAL ACTIVITIES

Certification

- Maryland Board of Physicians. Medical license #D0076388

ORGANIZATIONAL ACTIVITIES

Institution Administrative Appointments

- Chair, Housestaff Patient Safety and Quality Council, 2014-2015 (Johns Hopkins University)

Journal Peer Review (ad hoc)

- American Journal of Transplantation, 2015-present

Professional Societies

- American College of Surgeons, 2010-present
- American Society of Transplant Surgeons, 2013-present

RECOGNITION

Awards and Honors

- James Scholar Honors Program, 2003-2006 (University of Illinois)
- Phi Kappa Phi Honor Society, 2003 (University of Illinois)
- Phi Beta Kappa Honor Society, 2005 (University of Illinois)
- Merck Index Award for Excellence in Biochemistry, 2006 (University of Illinois)
- Magna Cum Laude, 2006 (University of Illinois)
- Most Outstanding Clinical Research Abstract, 2014 and 2015 (Johns Hopkins Department of Surgery Research)
- Top Poster Presentation, 2015 (American Society of Transplant Surgeons Winter Symposium)
- Young Investigators Award, 2016 (American Transplant Congress)

Invited Talks at Single Institutions

1. A Novel Approach to Increasing Live Donation: The Live Donor Champion Program. Medical University of South Carolina. April 2014.

2. The Live Donor Champion Program: Teacher Training Series. Johns Hopkins Comprehensive Transplant Center. August-September 2014.

3. Implementing the Live Donor Champion Program. Department of Transplantation, University of Chicago. December 2015.

4. Characterizing the Live Donor Evaluation Process. Johns Hopkins Comprehensive Transplant Center Living Donation Retreat. February 2016.

5. Clinical Research Methods. Department of Surgery, Johns Hopkins University. March 2016.

Invited Talks at National or International Meetings

1. The Proposal: Living Donation – The Live Donor Champion Program. American Society of Transplant Surgeons 16th Annual State of the Art Winter Symposium. Miami. January 2016.